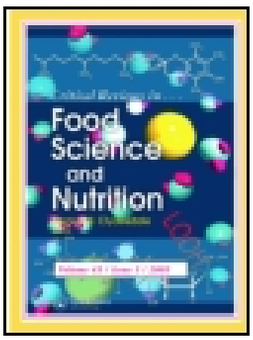

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

Polyphenols and obesity prevention: critical insights on molecular regulation, bioavailability and dose in preclinical and clinical settings

De Santis Stefania, M. L. Clodoveo, M. Cariello, G. D'Amato, C. Franchini, M. F. Faienza & F. Corbo

To cite this article: De Santis Stefania, M. L. Clodoveo, M. Cariello, G. D'Amato, C. Franchini, M. F. Faienza & F. Corbo (2020): Polyphenols and obesity prevention: critical insights on molecular regulation, bioavailability and dose in preclinical and clinical settings, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2020.1765736

To link to this article: https://doi.org/10.1080/10408398.2020.1765736

Published online: 21 May 2020.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2020.1765736

Taylor & Francis
Taylor & Francis Group

REVIEW

Polyphenols and obesity prevention: critical insights on molecular regulation, bioavailability and dose in preclinical and clinical settings

De Santis Stefania[a], M. L. Clodoveo[b], M. Cariello[b], G. D'Amato[c], C. Franchini[a], M. F. Faienza[d], and F. Corbo[a]

[a]Department of Pharmacy-Drug Science, University of Bari Aldo Moro, Bari, Italy; [b]Department of Interdisciplinary Medicine, University of Bari Aldo Moro, Bari, Italy; [c]Neonatal Intensive Care Unit, Di Venere Hospital, Bari, Italy; [d]Pediatric Unit, Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, Bari, Italy

ABSTRACT

Obesity represents one of the most important public health challenges of the 21st century and is characterized by a multifactorial etiology in which environmental, behavioral, metabolic, and genetic factors work together. Despite the rapid increase in prevalence of obesity in the last decades, especially in children, it remains a preventable disease. To battle obesity a multisector approach promoting healthier lifestyle in terms of physical activity and nutrition is needed. Specifically, biologically active dietary compounds, as polyphenols, are able to modulate the expression of genes involved in the development and progression of obesity and its comorbidities as demonstrated by multiple studies using different obesity models. However, human studies focusing on the transcriptomic modulation by polyphenols in obese patients are still limited and do not often recapitulate the results obtained in preclinical setting likely due to the underestimation of some variables such as bioavailability, dose and form (native vs. metabolized) of polyphenols used. The aim of this review is to summarize the state-of-art of nutrigenomic in vitro, in vivo and ex vivo studies as well as clinical trials based on dietary polyphenols to fight obesity. We also critical discuss the variables to be considered to fill the gap between preclinical and clinical settings.

KEYWORDS

Obesity; dietary polyphenols; bioavailability; inflammation; oxidative stress; nutrigenomics

1. Introduction

Obesity represents one of the most important public health challenges of the 21st century, reaching epidemic proportion worldwide and affecting adults, adolescents and children of both gender (Jaacks et al. 2019). An impressive data is that in the last four decades, there was more than a tenfold increase in the number of school-age and adolescents with obesity (WHO 2018). Moreover, obesity is associated with a higher rate of premature death due to the fact that obese patients are more likely to develop non communicable diseases (NCDs) (WHO 2018). This negatively impacts, in particular, on obese children developing NCDs at younger age, like cardiovascular diseases (Faienza et al. 2010, 2013), different types of cancer, metabolic and musculoskeletal disorders (Ciccone et al. 2016; Faienza et al. 2016, 2017; Marzano et al. 2018; Miniello et al. 2014; Weihrauch-Bluher, Schwarz, and Klusmann 2019). Specifically, several studies demonstrated a higher susceptibility to skeletal fractures in children affected by obesity, suggesting that adipose tissue affects bone metabolism (Faienza et al. 2019). To tackle the health implications of obesity, becoming more serious during childhood, European Union (EU) activated the Action Plan 2014–2020 program with the aim to halt the rise of overweight and obesity in children and adolescent people (0–18 years) by 2020 (EUActionPlan 2014). The Action Plan 2014–2020 proposes a population-based multi-disciplinary approach based on the promotion of a healthy lifestyle characterized by dietary regimen enriched in vitamins, minerals and other healthy micronutrients with a low content of fat and sugars, associated with an increased physical activity (EUActionPlan 2014).

As suggested by the Action Plan 2014–2020 along with recent publications (Collaborators 2019), diet and nutritionally bioactive compounds could have an active role in the modulation of the pathophysiology of different organs, even at molecular level, underlying the ability of these compounds to regulate the human transcriptome also in the adipose tissue (Pena-Romero et al. 2018). The relationship between nutrition and health was established a long time ago (Bleich et al. 2015); anyway during the last decades, bioactive compounds derived from food and plants have gained the interest of public and scientific communities for their ability to both maintain a health *status* and prevent disease's risk (Cory et al. 2018). Among these compounds, polyphenols derived from many components of the human diet are the leading ones; in fact, their potential preventive and therapeutic properties have been extensively investigated in many disorders such as cardiovascular disease, cancer, and inflammatory and metabolic diseases, including obesity

CONTACT M. F. Faienza mariafelicia.faienza@uniba.it Pediatric Unit, Department of Biomedical Sciences and Human Oncology, University of Bari Aldo Moro, 70124 Bari, Italy.

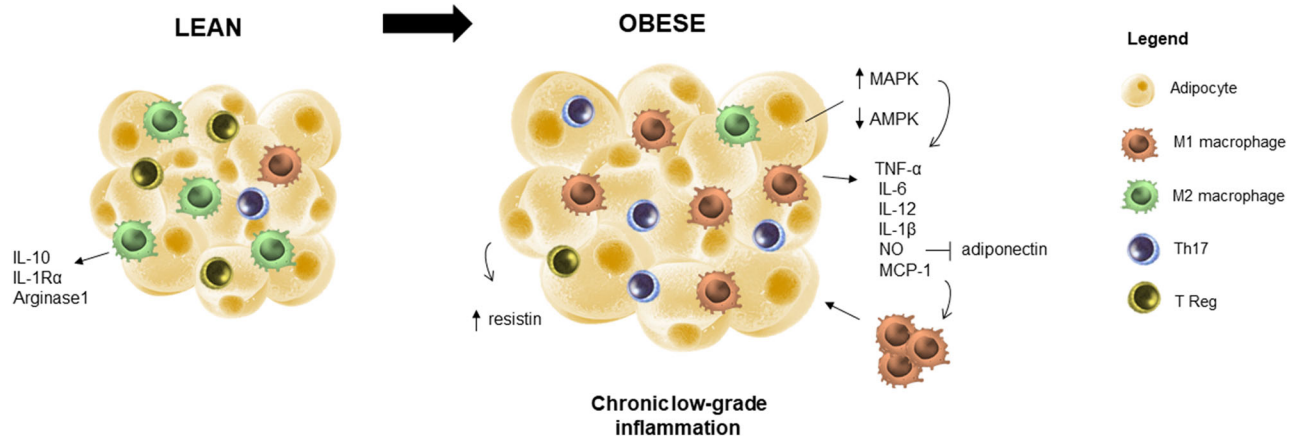

Figure 1. Chronic low-grade inflammatory state in obese patients. In obese patients there is an altered balance between pro- and anti-inflammatory mechanisms leading to an increased number of M1 pro-inflammatory macrophages, T helper 17 cell population (Th17) and a decreased number of T regulatory cells (T Reg) as compared to lean subjects. Moreover, the cytoplasmic activation of MAPK and the inhibition of AMPK pathways induce the transcription of pro-inflammatory cytokines, chemokines and oxidative stress molecules able to modulate adipokines expression thus perpetrating the inflammatory state.

(Faienza et al. 2020; Meydani and Hasan 2010). In the last case, the ability of distinct polyphenols classes to modulate all the intricate mechanisms supporting the onset and progression of obesity was postulated by numerous preclinical studies (Wang et al. 2014). However, more clinical studies are needed to verify the anti-obesity activity of dietary polyphenols in humans.

Given these data, in this review we analyzed all the mechanisms associated with obesity onset and progression, including inflammation and oxidative stress, that are regulated by dietary polyphenols. We also summarized the state-of-art of the nutrigenomic approach based on dietary polyphenols in the treatment of obesity showing results obtained from in vitro, in vivo and ex vivo studies, and in humans focusing of critical issues to be taken into account to fill the gap between preclinical and clinical settings.

2. Chronic low-grade inflammation in obesity development and progression

Obesity is the result of high dietary energy intake and low energy expenditure turning out as an energy imbalance and an increase in body weight (Walker et al. 2007). It is characterized by a low-grade chronic inflammatory condition in which there is a cross-talk between adipose tissue, inflammatory and metabolic pathways (Lee, Wollam, and Olefsky 2018). Cytokines, adipokines and reactive oxygen species (ROS) released from obese adipose tissue initiate a cascade of events leading to adipose tissue immune system activation coordinated by innate and adaptive components (Mathis 2013). In fact, adipose tissue, apart from being considered as an energy reservoir and a thermal regulator, is also a metabolically active endocrine organ (Kershaw and Flier 2004). Due to its endocrine function, adipose tissue modulates important processes as energy homeostasis, systemic insulin sensitivity and inflammation thanks to the secretion of cytokines and adipokines, such as plasminogen activator inhibitor type 1 (PAI-1) and resistin (Kalupahana, Moustaid-Moussa, and Claycombe 2012).

Normal metabolic functions of the adipose tissue are regulated by adipocytes and preadipocytes, and immune cells that collaborate to maintain a homeostatic condition. In fact, in lean individuals, adipose tissue contains small, insulin sensitive adipocytes and mostly alternatively activated macrophages (M2) with an anti-inflammatory phenotype induced by IL-10, IL-1 receptor antagonist (IL-1Rα), and arginase 1 secretion (Figure 1) (Lumeng, Bodzin, and Saltiel 2007). During obesity, this equilibrium is corrupted; the result is a shift toward a pro-inflammatory environment characterized by an increased number of neutrophils and monocytes that activate the adaptive immune response (Singer and Lumeng 2017). This activation, in turn, induce macrophage polarization toward a pro-inflammatory profile (M1) and insulin resistance (Odegaard and Chawla 2011). Macrophages M1 secrete a large amounts of pro-inflammatory cytokines, such as Tumor Necrosis Factor-α (TNF-α), Interleukin-6 (IL-6), IL-12, IL-1β, and chemokines, e.g. monocyte chemotactic protein-1 (MCP-1), as well as nitric oxide (NO) (Faienza et al. 2012). NO contributes to perturb the original equilibrium in adipose tissue down-regulating adiponectin, an adipokine with anti-inflammatory properties (Nacci et al. 2013). Chemokines increase the number of nonresident macrophages that are recruited into adipose tissue from remote sites under an inflammatory *stimulus* (Roth et al. 2011) (Figure 1).

Moreover, macrophages infiltration and activation and insulin resistance are regulated by distinct populations of the adaptive immune response. There is a specific balance of these cellular populations characterized by an increased number of T helper 17 cells (Th17) secreting the pro-inflammatory cytokine IL-17, T cytotoxic cells CD8 cells and B cells along with a decreased number of T regulatory cells (Treg) (Magrone and Jirillo 2015). In obese patients, the starting event of low-grade chronic inflammation at molecular level is the activation of adipose toll-like receptors (TLRs) by several dietary compounds like saturated fatty acids. TLRs activate mitogen-activated protein kinases (MAPKs) pathway inducing the adipocyte differentiation into large insulin resistant cells and the transcription of some

pro-inflammatory cytokines mediated by nuclear factor-κB (NF-κB) at molecular level (Bost et al. 2005). TLRs could also reduce the adenosine monophosphate-activated protein kinase (AMPK) activity that is associated with fatty acids (FA) metabolism (O'Neill, Holloway, and Steinberg 2013). The latter process contributes to the pro-inflammatory environment with up-regulation of adipogenesis or lipogenesis and the down-regulation of fatty acid β-oxidation.

Finally, alterations of gut microbiota also contribute to the maintenance of low-grade chronic inflammation in obese patients (Cox and Blaser 2013; Ridaura et al. 2013; Riva et al. 2017). Specifically, dysbiosis increases gut permeability due to the modulation of intestinal epithelial cell function and antimicrobial peptides (AMPs) production, and impairs the innate and adaptive immune responses (Burcelin 2016). A recent paper correlates an adaptive immune cell type, the T follicular helper (TFH) cells producing IgA, with the protection from obesity development in mice (Wang and Hooper 2019). By regulating IgA production, TFH cells restrain colonization by Desulfovibrio and promote colonization by Clostridia that protect against obesity, likely by limiting lipid absorption. This TFH function is mediated by the expression of *MyD88* (myeloid differentiation primary response protein 88) gene.

3: Nutrigenomic effects of polyphenols on in vitro, in vivo and ex vivo models of obesity

Obesity has a multifactorial etiology characterized by the interplay of environmental, behavioral, hormonal, metabolic, and genetic factors working together (Humbyrd 2018). Specifically, environmental factors, such as diet, have a bidirectional interaction with the genetic background. In fact, on one side, biologically active food components are able to modulate genes involved in the development and progression of obesity and its comorbidities (nutrigenomics) (Pena-Romero et al. 2018). On the other side, these phenomena could be regulated by the response dictated by the individual's genetic variations to food compounds (nutrigenetics) (Doo and Kim 2015). This last approach might shed a new light on personalized diet for the prevention and treatment of obesity (Ordovas et al. 2018). Nutrigenomics could be an effective preventive and therapeutic option too for this condition. In fact, many studies describe the ability of some food compounds, like polyphenols, vitamins, long-chain unsaturated fatty acids, and carotenoids to reduce the chronic inflammatory state characterizing obesity (Meydani and Hasan 2010). The ability of dietary compounds to promote human health through transcriptome modulation could also be extended to other pathological conditions, as in the case of intestinal inflammation (De Santis et al. 2017; Ducheix et al. 2018; Galleggiante et al. 2019).

According to the number of phenol rings present and the number and type of the structural binding element, polyphenols could be classified into different classes (Tsao 2010). Among these, stilbenes (resveratrol), flavonoids (catechins), flavonoids (anthocyanins from red pulp fruits), isoflavones (beans), curcuminoids (turmeric) and catechols (hydrohxytyrosol) were tested in some anti-obesity studies (Wang et al. 2014).

Dietary polyphenols could prevent the development of obesity by the following mechanisms that are summarized in Table 1, depicted in Figure 2 and listed below:

1. *increased lipolysis and fatty acid β-oxidation and decreased lipogenesis.* This important anti-adipogenic effect of polyphenols is mediated by the activation of AMPK. Activated AMPK phosphorylates and inactivates acetyle CoA carboxylase (ACC) thus inhibiting malonyl-CoA production with a resultant decrease of FA synthesis and an increase of their β-oxidation (Floyd et al. 2008). The limiting step for β-oxidation is the FA transport to the mitochondria by the protein carnitine palmitoyltransferase-1 (CPT-1) that is up-regulated after polyphenols treatment (Ejaz et al. 2009; Hao et al. 2010; Nagao et al. 2013; Wolfram et al. 2005). ACC inactivation also leads to reduction of lipid storage thanks to the suppression of FA esterification to triglyceride by inhibiting glycerol-3-phosphate acyl transferase-1 (GPAT-1) (Ejaz et al. 2009; Wolfram et al. 2005). Fat storage inhibition is also reached by decreasing the expression of the FA transporter CD36 located on the adipocyte membrane (Zhao et al. 2011). Furthermore, the intracellular signaling activated by polyphenols modulates the expression of several transcription factors such as sterol regulatory element-binding transcription factor 1c (SREBP1c) (Kim et al. 2011b; Rayalam et al. 2008; Wolfram et al. 2005), CCAAT-enhancer-binding protein α (C/EBPα) (Ejaz et al. 2009; Kim et al. 2011b; Rayalam et al. 2008), peroxisome proliferator-activated receptor alfa/gamma (PPAR-α/γ) (Costa et al. 2011; Ejaz et al. 2009; Floyd et al. 2008; Hao et al. 2010; Kang et al. 2010; Kim et al. 2011b; Rayalam et al. 2008; Zhang, Du, and Meng 2013; Zhao et al. 2011), liver X receptor (LXR) (Kim et al. 2011b) and their target genes i.e. fatty acid synthase (FAS) and lipoprotein lipase (LPL) (Floyd et al. 2008; Kim et al. 2011b; Rayalam et al. 2008; Wolfram et al. 2005; Monika et al. 2015), Stearoyl CoA desaturase 1 (SCD-1) (Klaus et al. 2005; Wolfram et al. 2005; Kang et al. 2016), fatty acid binding protein (aP2) (Kim et al. 2011b), hormone sensitive lipase (HSL) (Alberdi et al. 2011; Lee et al. 2009a; Rayalam et al. 2008), adipose triglyceride lipase (ATGL) (Lasa et al. 2012), and leptin (Kim et al. 2011b; Klaus et al. 2005; Wolfram et al. 2005) in adipose tissue (Figure 2);
2. *adipose tissue modulation.* Dietary polyphenols are involved in this process controlling the expression of many of the genes regulating the lipid metabolism. In fact, many studies reported an altered expression of PPARγ and C/EBPα (Carpi et al. 2019; Chen et al. 20092011,; Cho et al. 2007; Kim et al. 2011a; Kim et al. 2010; Lee, Kim, and Kim 2009b; Zhang et al. 2012), SREBP-1c (Chen et al. 2011; Lee, Kim, and Kim 2009b; Park et al. 2011; Zhang et al. 2012), FAS and LPL (Lee, Kim, and Kim 2009b; Park et al. 2011; Zhang et al.

Table 1. Transcriptomic studies describing the mechanisms of action of different polyphenols' classes in in vitro, in vivo and ex vivo models of obesity.

Anti-obesity effects	Mechanisms of action	Polyphenols	In vitro murine/human studies	In vivo murine/human studies	Ex vivo murine/human studies
Regulation of lipid metabolism	↓ PPARγ, C/EBPα, SREBP-1c, LXR, FAS, LPL, aP2, leptin TLR2/4, NF-kB, TNFα, IL-6 and others	Resveratrol		Epididymal WAT from: -C56BL/6 with HFD and 1% (Lee) cholesterol; -C56BL/6 with RSD (HFD + 0.4% RES) for 10 weeks (Kim et al. 2011b)	
	↑ ATGL	Resveratrol	3T3-L1/SGBS adipocytes + RES (100 μM) (Lasa et la. 2012)		
	↓ PPARγ, C/EBPα, SREBP-1c, FAS, LPL, HSL, ↑ UCP1 and others	Resveratrol	3T3-L1+ RES (25 μM) (Rayalam et al. 2008)		
	↓ HSL	Resveratrol		WAT from Sprague-Dawley rats on obesogenic diet: Ctrl and RES (30 mg/kg/d) for 6 weeks (Alberdi et al. 2011)	
	↑ PGC-1α and others	Resveratrol			MEFs from $SIRT1^{+/+}$ and $SIRT^{-/-}$ mice + RES (50 μM) (Lagouge et al. 2006)
	↓ Down-regulation of PPARγ transcriptional activity (aP2, LPL and others)	Resveratrol	3T3L-1 adipocyte + rosiglitazone (5 μM) or RES (50 μM) (Floyd et al. 2008)		
	↓ PPARγ ↑ SIRT1, FOXO1, and adiponectin	Resveratrol			WAT from obese patients + RES (1 μM) (Costa et al. 2011)
	↑ CPT1	Resveratrol		WAT from OLETF rats on control diet or RES diet (0.5%) for 4 weeks (Nagao et al. 2013)	
	↑ HSL	EGCG	3T3-L1+ EGCG (1, 10 μM) (Lee et al. 2009a)		
Regulation of lipid metabolism (continued)	↑ CPT1, PPARα/γ	Hydroxytyrosol	3T3-L1 + HT (0.1, 1, 10, 50 μM) (Hao et al. 2010)		
	↓ PPARγ and CD36	Curcumin	3T3-L1+ curcumin (10, 20 μM) (Zhao et al. 2011)		
	↑ CPT-1 ↓ GPAT-1, PPARγ, C/EBPα, VEGF-α and VEGFR2	Curcumin	3T3L-1 adipocyte + curcumin (5, 10, 20 μM) (Ejaz et al. 2009)	WAT from C56BL/6 with HFD (22%) +/− curcumin (500 mg/kg) for 12 weeks (Ejaz et al. 2009)	
	↑ CPT-1A/B, PPARα and others	PPC		PBMCs from moderately hyperlipidemic obese humans: low-fat yoghurt +/– PPC twice a day for 12 weeks (Radler et al. 2011)	
	↓ FASN, LPL, and leptin	EA		AT from Sprague Dawley rats fed with normal and HFD +/– HFEA for 11 weeks (Monika et al. 2015)	
	↑ CPT1, PPARα, LDLR and others	EA		Liver from KK-Ay mice fed with HFD +/–0.1% EA for 68 days (Yoshimura 2013)	
	↓ PPARγ, C/EBPα, SREBP-1c, FAS and aP2	Extract of lemon verbena plus Hibiscus flower		WAT from C57BL/6J HFD + MetA (50 e 100 mg/kg) vs. controls for 8 weeks (Lee et al. 2018)	
	↓ PPARγ ↑ Leptin	Apple polyphenols		Epididymal adipocytes from Wistar rats GFS + AP (700 mg/kg) for 8 weeks (Boque 2013)	
	↓ LPL, SCD-1, and others	EA		Liver from C57BL/6J fed with HF, HFHS or HFHS-R (0.03 % of EA) for 12 weeks (Kang et al. 2016)	
Adipose tissue modulation	↓ PPARγ, C/EBPα, SREBP-1c, adiponectin and leptin	Resveratrol	3T3-L1 pre-adipocytes + RES (10, 20, 40, 80 μM) (Chen et al. 2011)		

Adipose tissue modulation (continued)	↓ PPARγ, C/EBPα SREBP-1c, FAS, LPL aP2, and others	Resveratrol amplified grape skin extracts	3T3-L1 adipocytes + 50% and 80% ethanol extracts of RAGE (200, 400 μM) (Zhang et al. 2012)		
	↓ IL-6, PAI-1 ↑ Adiponectin, UCP2 and others	EGCG			Culture of subcutaneous preadipocytes isolated from AT of healthy woman + C3G and Cy (100 mM) (Tsuda et al. 2006)
	↓ PPARγ, C/EBPα, SREBP-1c, FAS, LPL, aP2, resistin, leptin and others ↑ HSL, ATGL, CPT-1 and UCP2	EGCG		Epididymal WAT from C57/Bl6 mice on HFD for 8 weeks. Randomization: HFD +/–0.2% (w/w) or 0.5% (w/w) TEAVIGO® for 8 weeks (Lee et al. 2009b)	
	↓ Leptin, SCD-1 and others	EGCG		Epididymal WAT from NZB mice on HFD + 0.5 and 1% (w/w) TEAVIGO® for 4 weeks (Klaus et al. 2005)	
	↑ FAS, SREBP-1c, GPAT, SCD-1, leptin, and others ↑ CPT-1	EGCG		Epididymal WAT from C57BL/6J mice on HFD +/– 1% (w/w) TEAVIGO® for 20 weeks (Wolfram et al. 2005)	
	↓ PPARγ and C/EBPα	EGCG	3T3-L1+ EGCG (10 μM) or NAC (10 mM) (Kim et al. 2010)		
	↑ PPARγ and UCP2	Tea polyphenols		WAT from Sprague Dawley rats on HFD + GT, BT and EGCG for 27 weeks (Chen et al. 2009)	
	↓SREBP-1c, FAS, SCD -1 and HSL	TGE		WAT from *ob/ob* mice + 0.5, 1% TGE for 6 weeks (Park et al. 2011)	
	↑ PPARγ, C/EBPα and adiponectin	(-)-catechin	3T3-L1 pre-adipocytes + 50μM (–)-catechin (Cho et al. 2007)		
	↓ ap2	Curcumin	3T3L-1 + curcumin (25 μM) (Ahn et al. 2010)		
	↓ PPARγ, C/EBPα, leptin, adiponectin and resistin	Curcumin	3T3-L1 pre-adipocytes + curcumin (10, 20, 30 μM) (Kim et al. 2011a)		
Adipose tissue modulation (continued)	↑SIRT1, AMPKα, FOXO1 and others ↓ PPARγ, FAS and others	Resveratrol			Bovine intramuscular adipocytes + 0, 100, 200, 400 μm RES for 48h (Liu et al. 2018)
	↑ G6PC, IGFBP1 and PEPCK	Resveratrol	H4IIE rat hepatoma cells + 400 μm RES (Frescas et al. 2005)		
Insulin sensitivity regulation	↑ PPARγ, FAS, LPL, GLUT4, adiponectin ↓ Leptin and others	GPEP	3T3-442A pre-adipocytes + GPEP (125, 250, 500 μg/ml) (Torabi and DiMarco 2016)		
	↓ SREBP-1c, PEPCK and others	Resveratrol		Liver-C57BL/KsJ-db/db mice fed with RES (0.02% w/w) for 6 weeks (Do et al. 2012)	
	↑ INSR, IRS-1, IRS-2 Akt2 and Glut4	Polyphenol-rich ethyl acetate fraction from Molineria latifolia		Skeletal muscle from Sprague-Dawley rats fed with this fraction (200 mg/kg BW) (Ooi et al. 2018)	
	↑ IRS-1, PI3Kp85 and Glut-4	Folium Mori Extract		Skeletal muscle from Sprague-Dawley rats fed with the extract (2 g/kg BW) (Cai et al. 2016)	
Reduced low grade-chronic inflammation	Reverse the modulation of IL-6, IL-8, IL1-β, MCP-1, PAI-1 and adiponectin mediated by IL-1β	Resveratrol			Human AT with IL-1β (2 ng/ml) +/– RES (50 μM) (Olholm et al. 2010)

(*continued*)

Table 1. Continued.

Anti-obesity effects	Mechanisms of action	Polyphenols	In vitro murine/human studies	In vivo murine/human studies	Ex vivo murine/human studies
	Reverse the modulation of adiponectin and PPARγ mediated by TNF-α	Resveratrol	3T3-L1 adipocytes + RES (5, 10, 20, 50 μM) + TNF-α (20 ng/mL) (Zhang et al. 2013)		
	↓ TNFα, IL-6 and resistin ↑ adiponectin, PPARγ	Resveratrol	3T3-L1 adipocytes + macrophage-derived CM + RES (0.1, 1, 10μM) RAW264.7 cells + RES (0.1, 1, 10 μM) (Kang et al. 2010)		
Reduced low grade-chronic inflammation (continued)	↓ MCP-1 and IL-6 ↑ adiponectin	Resveratrol	3T3-L1+ RES (10, 25, 50 μM) + TNF-α (10 ng/mL) (Zhu et al. 2008)		
	↓ Resistin	EGCG	3T3-L1+ EGCG (5, 20, 100 μM) (Liu et al. 2006)		
	↓ TNFα, IL-β, IL-6 and COX-2	Curcumin and Resveratrol	3T3L-1 adipocyte + curcumin or RES (both at 5, 10, 15, 20 μM) (Gonzales and Orlando 2008)		
	↓ TNFα, IL-6	Curcumin	3T3-L1 + curcumin (5, 10, 20 μM) (Wang et al. 2009)		
	↑Adiponectin, SIRT1, FOXO1 and others ↓F4/80	Curcumin		WAT from C56BL/6 mice with 4% or 35% fat by weight +/− 3% by weight of curcumin for 10 weeks. WAT from *ob/ob* mice with 4% fat by weight +/− 3% by weight admixture of curcumin for 6 weeks (Weisberg et al. 2008)	
	↓ TNFα	Three different sweet cherry extracts			PBMCs cultures from obese children + polyphenol from Giorgia, Bigarreau, and Ferrovia extracts (100 μg/ml) (Corbo et al. 2019)
	↓ MCP-1, IL-1β, COX2, SOD2, GPX, VEGF and others ↑ PPARγ	Oleocanthal and Oleacein	SGBS preadipocytes + OC/OA (25 μM) + TNF-α (10 ng/mL) (Carpi et al. 2019)		
Reduced low grade-chronic inflammation (continued)	↓ MCP-1, IL-6, IL-1β, COX2, SOD1, GPX, VEGF and others ↑ PGC-1α and GLUT4	Hydroxytyrosol	SGBS preadipocytes + HT (1, 10 μM) + TNF-α (10 ng/mL) (Scoditti et al. 2019)		
	↓ pathways related to oxidative stress, inflammation, immune defense and others	EGCG + RES		SAT from overweight and obese humans with EGCG + RES (282 mg/d, 80 mg/d) or placebo for 12 weeks (Most et al. 2018)	
	↓ IL-1β, LEPR and others	Green tea polyphenols		Liver from Sprague Dawley rats HFD +/− 0.5%GTP (wt/vol) vs. control diet for 8 month (Lu 2012)	
	↓ TNFα, IL-6, MCP-1 and others	Anthocyanins		Epididymal AT from C57Bl/6J mice fed with HFD +/− 4% (wt/wt) blueberry vs. control diet for 8 weeks (DeFuria 2009)	
	↓ production of reactive oxygen species and leukocyte activation	High-polyphenol cocoa powder		PBMCs from healthy human + 1.3 g cocoa pills (50% polyphenols) for 2 hours (Barrera-Reyes et al. 2019)	
	↓ TNFα, IL-6, MCP-1, F4/80 and others	EA		Epididymal AT from C57BL/6J fed with HF, HFHS or HFHS-R (0.03 % of EA) for 12 weeks (Kang 2016)	
	↓ pathways related to inflammation	VOO polyphenols		PBMCs from patients with MetS + acute administration of VOO with high and low polyphenol content (Camargo et al. 2014)	

	↓ IL-6, IL-1 and CXCL-1	VOO polyphenols		PBMCs from patients with MetS + acute administration of VOO with high and low polyphenol content (Camargo et al. 2010)
Energy expenditure and thermogenesis	↑ UCP2	EGCG	3T3-L1+ EGCG (1, 5, 10 μM) (Lee et al. 2009c)	
	↑ UCP1 and PGC-1α	Theaflavins		BAT from ICR mice fed with 10 mg/kg TF or 4 ml/kg distilled water orally for 2 days (Kudo 2015)
	↑ UCP1, UCP2 and PGC-1α	EGCG		BAT from C57Bl/6J mice fed with HFD +/− 0.2% EGCG (w/w) for 8 weeks (Lee et al. 2017)
	↑ UCP1, SIRT1 and others			BAT from mice fed with standard diet +/− RES (4 g/kg) for 8 weeks (Andrade et al. 2014)
	↑ UCP1 and PGC-1α	Berberine		i.p. injection of BBR in db/db mice for 4 weeks (Zhang et al. 2014)
	↓ energy metabolism, lipid metabolism, proliferation, inflammation and cancer pathways	EVOO polyphenols		PBMCs from patients with MetS and healthy subjects + acute administration of EVOO with high polyphenol content (D'Amore et al. 2016)
	↑ SIRT1, UCP1, PGC-1α and others	Resveratrol		SAT from FVB/N mice fed with standard diet or HFD +/− RES (400 mg/kg) for 8 weeks. SAT from volunteers with type 1 obesity treated with 500 mg trans-RES or placebo for 4 weeks (Andrade et al. 2019)

Abbreviations: apple polyphenols (AP), berberine (BBR), black tea (BT), carnitine palmitoyltransferase-1 (CPT-1), cyaniding (Cy), adipose triglyceride lipase (ATGL), CCAAT-enhancer-binding protein alfa (C/EBPα), conditioned medium (CM), cyanidin 3-O-β-D-glucoside (C3G), cyclooxygenase-2 (COX-2), (C-X-C motif) ligand 1 (CXCL1), ellagic acid (EA), epigallocatechin gallate (EGCG), extra virgin olive oil (EVOO), fatty acid binding protine (aP2), fatty acid synthase (FAS), forkhead box protein O1 (FOXO1), glucose-6-phosphatase (G6PC), glycerol-3-phosphate acyl transferase-1 (GPAT-1), grape powder extracted polyphenols (GPEP), green tea extract (GTE), green tea polyphenols (GTP), HF diets containing no-sucrose (HF), HF diets containing high-sucrose (HFHS), HF diets containing high-sucrose plus EA (HFHS-R), hydro-alcoholic fruit extract of avocado (HFEA), high-fat-sucrose (HFS), high-fat diet (HFD), insulin-like growth factor-binding protein 1 (IGFBP1), hormone sensitive lipase (HSL), hydroxytyrosol (HT), insulin receptor (INSR), insulin receptor substrates 1 (IRS-1 and IRS-2), interleukin-6 (IL-6), intraperitoneal injection (i.p.), leptin receptor (LEPR), lipoprotein lipase (LPL), liver X receptor (LXR), Metabolaid® (MetA): combination of lemon verbena and hibiscus-flower extracts, metabolic syndrome (MetS), monocyte chemotactic protein-1(MCP-1), mouse embryonic fibroblasts (MEFs), N-acetylcysteine (NAC), New Zealand black (NZB), nuclear factor kappa B (NF-kB), oleocanthal (OC), oleacein (OA), otsuka Long-Evans Tokushima fatty (OLETF) rats, peripheral blood mononuclear cell (PBMC), phosphoenolpyruvate carboxykinase (PEPCK), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), peroxisome proliferator-activated receptor alfa and gamma (PPARα and PPARγ), combination of low-dose PUFAs, polyphenols and L-carnitine (PPC), plasminogen activator inhibitor type-1 (PAI-1), resveratrol (RES), resveratrol-amplified grape skin extract (RAGE), resveratrol-supplemented diet (RSD), subcutaneous adipose tissue (SAT), silent mating type information regulation 2 homolog (SIRT1), Simpson-Golabi-Behmel syndrome (SGBS), stearoyl CoA desaturase-1 (SCD-1), sterol regulatory element-binding transcription factor-1c (SREBP-1c), theaflavins (TF), toll-like receptor 2 and 4 (TLR2/4), tumor necrosis factor α (TNFα), uncoupling protein 1 and 2 (UCP1 and UCP2), vascular endothelial growth factor receptor 2 (VEGFR2), vascular endothelial growth factor α (VEGFα), virgin olive oil (VOO), white adipose tissue (WAT).

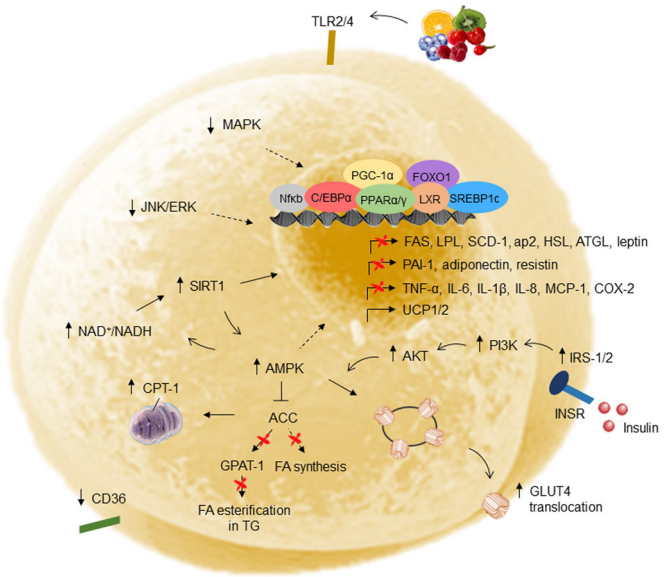

Figure 2. Molecular mechanisms of dietary polyphenols in adipocyte from obese patients. Nutritionally active compounds are able to modulate multiple cytoplasmic pathways that directly (solid lines) and indirectly (dashed lines) regulate the expression of distinct transcriptional factors working independently, except for PGC-1α and PPARα/γ. These modulations result in the repression of genes involved in lipid and adipose tissue metabolism as well as inflammation and in the induction of genes regulating thermogenesis. Moreover, the up-regulation of AMPK inhibits FA synthesis and esterification in triglyceride (TG), induces β-oxidation by increasing CPT-1 expression in the mitochondria and increases GLUT4 translocation. GLUT4 translocation could also be induced by the increased expression of insulin receptor (ISNR), insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), PI3K and AKT axis. Fat storage is also inhibited after polyphenols treatment by the reduction in CD36 expression level.

2012), SCD-1 (Klaus et al. 2005; Park et al. 2011), aP2 (Ahn et al. 2010; Zhang et al. 2012), HSL (Park et al. 2011), ATGL and CPT-1 (Lee, Kim, and Kim 2009b). Moreover, the expression of some adipokines indicates the contribution of these molecules in this process (Chen et al. 2011; Cho et al. 2007; Kim et al. 2011a; Lee, Kim, and Kim 2009b; Tsuda et al. 2006) (see below). The effects of polyphenols in adipose tissue modulation are varied and each polyphenol activates different pathways. Catechins, contained in green tea, induce the β-oxidation modulating the expression of PPARγ and FAS in adipose tissue. At the same time, catechins increase the expression of CPT-1 that allows fatty acids transport into mitochondria (Lee, Kim, and Kim 2009b). Resveratrol is also involved in the modulation of β-oxidation up-regulating the AMPK activity that activates fatty acid oxidation, suppresses hepatic gluconeogenesis and improves insulin sensitivity (Chung, Manganiello, and Dyck 2012). Furthermore, it has been demonstrated that resveratrol modulates PPARγ expression and inhibits malonyl-CoA synthesis, a precursor of fatty acid synthesis (Aguirre et al. 2014; Chen et al. 2011; Zhang et al. 2012). Anthocyanins, contained in strawberries, blueberries, blackberries, blood oranges and apples, are able to modulate AMPK synthesis regulating fatty acids β-oxidation even if their mechanisms of action are not acting at molecular level (Wu et al. 2013). Hydroxytyrosol, the main EVOO polyphenol, down-regulates the expression of PPAR α and γ and increases AMPK and lipase gene expression leading to an inhibition of adipocytes differentiation and a reduction in adipocyte size and body weight (Hao et al. 2010; Peyrol, Riva, and Amiot 2017).

The differentiation process of pre-adipocytes into mature adipocytes is mediated by the repression of some adipocyte differentiation biomarkers expression, such as PPARγ, C/EBPα and aP2 and the induction of Sirtuin 1 (SIRT1) and forkhead box protein O1 (FoxO1) expression (Kim et al. 2010; Weisberg, Leibel, and Tortoriello 2008). These effects are mediated by both AMPK and SIRT1 activities that are tightly interconnected (Canto et al. 2009; Chen et al. 2011; Fullerton and Steinberg 2010). In general, SIRT1 and AMPK exert a key role in several cellular process. Sirtuins are a family of NAD^+-dependent deacetylases and ADP-ribosyltransferases involved in DNA repair and metabolic regulation (Baur et al. 2010; Donmez and Guarente 2010). Polyphenols, specifically resveratrol, are able to activates SIRT1 promoting mitochondrial biogenesis via the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) (Gerhart-Hines et al. 2007; Rodgers et al. 2005). Furthermore, resveratrol activates also AMPK. There is a dynamic interaction between SIRT1 and AMPK. It has been shown that AMPK activates SIRT1 indirectly up-regulating the levels of SIRT1 co-substrate NAD^+ (Canto et al. 2009; Fulco and Sartorelli 2008). On the other hand, resveratrol could induces SIRT1 leading to AMPK activation via deacetylation of the AMPK kinase LKB1 (Hou et al. 2008; Ivanov et al. 2008; Lan et al. 2008). Catechins, resveratrol and curcumin reduce fat accumulation in adipocytes via the activation of AMPK-SIRT1 pathway at molecular and protein level (Costa et al. 2011; Lagouge et al. 2006; Rayalam et al. 2008; Weisberg, Leibel, and Tortoriello 2008). Moreover, catechins modulate adipocytes differentiation activating AMPK, a suppressor of PPARγ and C/EBPα expression (Chan et al. 2011). Resveratrol activates AMPK and SIRT1 leading to the inhibition of PPARγ and ACC. In 3T3L1, curcumin phosphorylates and activates AMPK down-regulating ACC (Ejaz et al. 2009; Lee et al. 2009d).

Notably, the role of FoxO1 in adipogenesis is controversial and needs some clarifications. The main polyphenols links to FoxO1 pathway are catechins and resveratrol. Kim et al. demonstrated that EGCG treatment of 3T3L1 cells activates the phosphorylation of FoxO1 protein reducing its transcriptional activity and fat accumulation (Kim et al. 2010). On the contrary, in a dose-dependent manner, resveratrol inhibits the expression of several genes like PPARγ, C/EBPα, and aP2 activating the expression of AMPK, SIRT1 and FoxO1. In particular, SIRT1 deacetylates and activates FoxO1 that binds to the PPARγ promoter site and prevents its transcription decreasing adipocytes

proliferation (Harp 2004). In bovine intramuscular adipocytes, resveratrol activates SIRT1-AMPK-FoxO1 pathway causing dephosphorylation and nuclear translocation of FoxO1 suppressing PPARγ expression and fatty acid synthesis (Liu et al. 2018). Furthermore, it has been demonstrated that resveratrol induces apoptosis in brown adipocytes via FoxO1. Specifically, the activation of Sirt1 by resveratrol deacetylates FoxO1 and renders it immobile within the nuclear compartment thus promoting FoxO1-dependent transcription (Frescas, Valenti, and Accili 2005). In brown adipocytes, resveratrol leads to AKT/PKB phosphorylation and FoxO1 dephosphorylation/deacetylation in parallel with FoxO1 nuclear accumulation inducing apoptosis (Liu et al. 2018).

Polyphenols could also down-regulate the growth and the expansion of adipocytes inducing G0/G1 and G2/M cell cycle arrest (Chan et al. 2011; Hung et al. 2005; Kwon et al. 2012) and apoptosis as shown by caspase-3 activation (Chen et al. 2012);

3. *modulation of insulin sensitivity*. Some polyphenols could modulate this process by the regulation of glucose uptake in adipocytes (Kang et al. 2019). AMPK, apart from regulating FA metabolism in obesity environment, is able to modulate the glucose transport (Lin and Hardie 2018). Specifically, AMPK activation could increase the uptake of glucose through GLUT4 translocation (Yamaguchi et al. 2005) thus leading to the reduction of insulin resistance, a clinical condition characterizing obesity and obesity-related diseases as Type 2 Diabetes Mellitus (T2DM) (DeFronzo et al. 2015). Moreover, polyphenols could modulate glucose uptake increasing GLUT4 expression by the activation of AKT pathways and the down-modulation of PPARγ transcriptional activity (Scoditti et al. 2019; Torabi and DiMarco 2016). In fact, insulin signaling is mediated by a cascade of events initiated by the binding of insulin to its receptor inducing phosphorylation of insulin receptor substrates (IRSs) on tyrosine residues. This binding activates PI3K/AKT pathways triggering the translocation of GLUT4 to the plasma membrane (Figure 2). Under hyperglycemic and elevated FFA conditions, the overproduction of ROS activates Nf-κB and stress transduction pathways, such as JNK, that initiate serine phosphorylation of IRS-1 thereby inhibiting Akt/PI3K activation and, in turn, GLUT4 translocation. This inhibitory signal reduces insulin sensitivity and disrupts cellular glucose uptake, leading to insulin resistance. Polyphenols could increase insulin sensitivity and improve glucose uptake by activating the IRS-1/PI3K/GLUT4 axis at molecular level as demonstrated by the administration of ethyl acetate fraction (EAF) isolated from the rhizome of *Molineria latifolia* (Ooi et al. 2018) and of Mulberry leaf (Folium Mori) (Cai et al. 2016) in in vivo studies on rats. Moreover, obesity and T2DM could also be the result of elevated levels of FFA leading to ectopic fat deposition in hepatocytes that inhibits the AKT/PI3K cascade. This inhibition induces insulin resistance through the reduction of GLUT2 expression and hyperglycemia by increasing hepatic glucose production. In fact, inhibition of AKT/PI3K cascade decreases the phosphorylation of FoxO1 that activates the transcription of rate-limiting enzymes for gluconeogenesis, i.e. glucose-6-phosphatase (G6PC) and phosphoenolpyruvate carboxykinase (PEPCK) (Frescas, Valenti, and Accili 2005). The anti-obesity effects of some polyphenols, such as resveratrol, could also be exerted by their ability to down-modulate the expression of hepatic gluconeogenic genes like SREBP-1c and PEPCK by activating AMPK and its downstream targets in liver tissues (Do et al. 2012);

4. *reduction of the inflammatory response and the oxidative stress*. Polyphenols are able to dampen the low grade-chronic inflammatory state typical of obesity by down-modulating the expression of pro-inflammatory cytokines and chemokines acting on upstream signal molecules, such as NFκB, ERK and JNK, in the adipose tissue (Gonzales and Orlando 2008; Kang et al. 2010; Olholm et al. 2010; Wang et al. 2009; Zhu et al. 2008). Specifically, the down-modulation of chemokines in adipose tissue induces a decreased recruitment of M1 macrophages thus contributing to the reduction of the inflammatory state due to the ability of M1 macrophages to secrete pro-inflammatory cytokines (Weisberg, Leibel, and Tortoriello 2008; DeFuria et al. 2009; Kang et al. 2016; Lu et al. 2012). Dietary polyphenols are also able to down-regulate some pro-inflammatory adipokines (e.g. PAI and resistin) (Kang et al. 2010; Liu et al. 2006; Olholm et al. 2010), and to increase adiponectin expression level (Kang et al. 2010; Olholm et al. 2010; Weisberg, Leibel, and Tortoriello 2008; Zhang, Du, and Meng 2013; Zhu et al. 2008). Adiponectin increase could also be mediated by the up-regulation of SIRT1 (Qiao and Shao 2006; Weisberg, Leibel, and Tortoriello 2008). Moreover, the anti-oxidative effect of some dietary polyphenols in obesity is mediated by the regulation of the expression of genes involved in the oxidative stress process e.g. the enzyme cyclooxygenase-2 (COX-2), superoxide dismutase (SOD1/2) and glutathione peroxidase (GPX) (Carpi et al. 2019; Gonzales and Orlando 2008; Scoditti et al. 2019). These anti-oxidant effects were also found when polyphenols from EVOO were used in *in vitro* models of obesity thus underlying the nutraceutical properties of this food (De Santis et al. 2019);

5. *stimulation of energy expenditure by inducing thermogenesis in brown adipose tissue (WAT)*. BAT and white adipose tissue (Kang) exert different functions; BAT is a thermogenic tissue while WAT is a fat-storing tissue (Scherer 2006). BAT is able to dissipate large amounts of stored energy as heat activating the brown-fat-specific uncoupling protein 1 (UCP1). Specifically, thermogenesis in BAT is mediated by an increase in the expression of PGC-1α, likely induced by SIRT1, that activates PPAR-α/γ thus enhancing the expression of uncoupling protein 1 and 2 (UCP1 and UCP2) (Barbera et al. 2001;

Chen et al. 2009; Lee, Kim, and Kim 2009b; Lee and Kim 2009c; Rayalam et al. 2008; Scoditti et al. 2019; Tsuda et al. 2006). Disruption of BAT homeostasis occurs with age and increased body weight. Several studies showed the role of polyphenols in the modulation of energy expenditure. It has been demonstrated that in mouse model, a single dose of theaflavins increases energy expenditure inducing the gene expression of UCP1 and PGC-1α in BAT (Kudo et al. 2015). In BAT of obese mice, EGCG administration regulates thermogenesis and mitochondrial biogenesis via AMPK activation (Lee et al. 2017). Mice treated with resveratrol for 8 weeks increased BAT UCP1 and SIRT1 gene expression improving energy expenditure (Andrade et al. 2014). In a mouse model of obesity, berberine, a polyphenol derived from medical plants, stimulates BAT inducing thermogenic markers like UCP1 and PGC-1α and improves cold tolerance (Zhang et al. 2014).

As discussed elsewhere, it is important to note that dietary polyphenols also participate in the regulation of obesity modulating the gut microbiota (Anhe et al. 2015; Kumar Singh et al. 2019; Roopchand et al. 2015). In fact, dysbiosis could impact on metabolic pathways influencing obesity acting at molecular level on different mechanisms including bile salt metabolism, short-chain fatty acids, and metabolic endotoxemia (Barathikannan et al. 2019). Dysbiosis-induced dysregulation of multiple processes in the context of obesity supports the use of probiotics. It was demonstrated that probiotic administration induced weight loss both in animal and human studies (Barathikannan et al. 2019).

The ability of dietary polyphenols to modulate the mechanisms described before at molecular level is depicted in Figure 2 and reported in Table 1 that summarizes the studies conducted on in vitro, in vivo and ex vivo models of obesity by using different polyphenols. Contradictory results arising from some of the reported studies as in the case of the increased expression reported for adipogenic genes such as PPARγ, FAS and LPL after grape powder extracted polyphenols (GPEP) administration to 3T3-442A pre-adipocytes, along with GLUT4 up-modulation (Torabi and DiMarco 2016). This controversial results could be explained by the ability of GPEP to induce adipocyte differentiation via the up-regulation of GLUT4 and adipogenic genes. In fact, the activation of PPARγ promotes terminal differentiation of adipocytes through up-regulation of adipogenic target genes. Several studies indicated a relationship between the activation of PPARγ pathway and insulin sensitivity; this relationship resulted in an increased glucose uptake (Torabi and DiMarco 2016). Moreover, mutations in PPARγ in both rodents and humans were associated with insulin resistance (Agostini et al. 2006; He et al. 2003). On the other hand, the healthy effect of GPEP was also supported by the ability to prevent adipocyte hypertrophy i.e. the progression of small functional differentiated adipocytes to dysfunctional large ones, by inducing lipolysis through AMPK phosphorylation (Torabi and DiMarco 2016).

More in general, the contrasting data reported in Table 1 could be also likely explained by discordance in terms of study models or polyphenols (type and/or concentration) used in the experiments. To overcome these discrepancies, further studies are needed to evaluate their effective modulation in the contest of obesity. Furthermore, we observed that many of the molecular modulations induced by dietary polyphenols in terms of lipid metabolism and adipose tissue modulation refers to common genes (Table 1). More in general, this could be extended to all the mechanisms listed supporting the idea that polyphenols orchestrated a plethora of tightly interconnected beneficial effects in order to fight obesity.

As reported in Table 1, many of the in vitro studies were conducted on 3T3-L1 cells likely due to the fact that this line represents the best characterized in vitro model to study obesity. Anyway, 3T3-L1 cells could not be relevant for the study of polyphenols' bioactivity in terms of host and microbial metabolism. In fact, the broadly used in vitro model to study the uptake and metabolism of the polyphenolic compounds found in the diet are the intestinal and hepatic cells (Del Rio et al. 2013). Due to the fact that metabolic processes in in vitro models seem to be cell type- and compound-specific, cells not directly linked to the digestive system could not contribute quantitatively to the bioavailability data of phenolic compounds, as in the case of 3T3-L1 (Aragonès et al. 2017). For this reason, it could be better to focus on outcomes from in vivo studies also because in vitro studies on polyphenols that doesn't take into account the metabolic reactions, could eventually analyze molecules which are not found in vivo or have concentrations different from those normally achieved with diet (Serreli and Deiana 2019).

The in vivo studies testing the modulation of gene expression by dietary polyphenols on obesity and its correlated diseases were performed on genetic- and diet-induced models (Table 1). Anyway, diet-induced models of obesity were more commonly used to evaluate the molecular expression after polyphenols administration relative to the genetic-induced models of obesity. These models were based on the animal feeding with high fat diet (also enriched with cholesterol or high sucrose content) alone and with polyphenols supplementation to understand the effects of such compounds in the modulation of the critical pathways involved in obesity onset and progression at molecular level.

4: Human studies on obesity using a nutrigenomic approach based on dietary polyphenols

Human studies on nutrigenomic effects of dietary polyphenols are very limited and most of them are performed on adults (Table 1). To our knowledge, the only one nutrigenomic study on pediatric obesity is the ex vivo study describing the ability of sweet cherry extracts containing multiple polyphenols to reduce spontaneous osteoclastogenesis in cultures of peripheral blood mononuclear cells (PBMCs) from obese children. In fact, as reported above, obesity is frequently associated with a high incidence of

bone fractures. The results of this study are mediated by the reduction of TNFα expression without negative effects on cell viability (Corbo et al. 2019). Regardless the paucity of clinical trials on childhood obesity, an European multicenter study underlined the possibility to use the expression level of genes such as CPT1A and LEPR (Leptin Receptor) in blood cells as markers of insulin-resistant or dyslipidemic state associated with obesity (Sanchez et al. 2012).

Regarding the in vivo nutrigenomic studies on adults, a microarray analysis on subcutaneous adipose tissue showed that epigallocatechin-gallate and resveratrol supplementation for 12 weeks in overweight and obese men and women induced a downregulation of genes related to inflammation, immune system, energy metabolism and adipocyte turnover (adipogenesis and apoptosis/autophagy). Nevertheless, it remains to confirm these findings at transcriptional and functional level trying to explain how these molecular modulations can be translated in beneficial metabolic changes. In fact, supplementation of this polyphenols combination did not induce any significant effects on body composition, AT morphology, lipolysis and insulin sensitivity (Most et al. 2018). Another in vivo studies demonstrated that the consume of low-fat yoghurt enriched with a combination of low-dose PUFAs, polyphenols and L-carnitine (PPC) twice a day for 12 weeks upregulated the expression of genes involved in fatty acid oxidation in PBMCs of moderately hyperlipidemic obese humans (Radler et al. 2011).

Moreover, some other clinical studies reporting the ability to modulate energy expenditure and fatty acid oxidation in patients with obesity or obesity-related disease as metabolic syndrome (MetS) were reported (Bo et al. 2020). In fact, as described before for in vitro and in vivo studies, polyphenols could induce an anti-obesity effect thanks to their ability to promote energy dissipation by activating brown adipose tissue also in clinical studies. This may represent an alternative polyphenols-mediated strategy to promote weight loss. A recent study demonstrated that the oral administration of resveratrol is associated with an increased thermogenesis in the subcutaneous adipose tissue of both mice and humans. The molecular regulation supporting this result is the high expression of some genes regulating the thermogenic program such as SIRT1, UCP1 and PGC1α (Andrade et al. 2019). Moreover, patients with MetS, administered with an acute intake of EVOO, are able to modulate energy homeostasis and fatty acid oxidation, even if they acted at lesser extent relative to healthy controls (D'Amore et al. 2016). These studies support the idea that some benefic effects of polyphenols might go beyond their widely studied anti-oxidant and anti-inflammatory effects as in the case of patients with MetS administered with an acute intake of olive oil enriched with a different content of polyphenols (Camargo et al. 2010; Camargo et al. 2014) or healthy human administered with an acute intake of high-polyphenol cocoa powder (Barrera-Reyes et al. 2019). Anyway, as reported for animal studies in this context (Mele et al. 2017), some discrepancies could also be extended to the clinical setting. For example, supplementation with ephedrine and caffeine for four weeks in premenopausal morbidly obese women, induces body weight loss even if this results are not associated with changes in the gene expression suggesting the involvement of other mechanisms (Bracale et al. 2014). Thus, more work is needed to characterize the biologic effects of polyphenols in the context of energy expenditure and BAT activation in humans.

Apart from polyphenols, also modified fat/caloric diets as well as probiotics, β-D-glucans, Omega-3 and vitamin D were studied relative to their ability to modulate gene expression in the context of obesity in humans and reviewed elsewhere (Paipilla et al. 2016).

As reported in Table 1, the focus on nutrigenomics highly restricted the number of human studies to be considered even if a huge number of clinical trials on obesity were performed using dietary polyphenols as reviewed elsewhere (Castro-Barquero et al. 2018; Huang et al. 2014). Table 2 provides a summary of the clinical trials on obesity classified based on trial phase, study design, outcomes and results, when reported. The updated list of the clinical trials also showed that the study of the dietary polyphenols' impact on obesity was extended to comorbidities commonly found in obese patients such as cardiovascular disease, T2DM and MetS (Table 2). All of these studies mainly reported data regarding anthropometric parameters, biochemical analysis and serum biomarkers, without gene expression quantification. Moreover, the indicated studies also supported the use of these compounds for the management of body weight, a clinical feature of obese patients. More in general, some human studies indicate the ability of nutraceutical agents from plants like *Cissus quadrangularis*, *Citrus aurantium* and *Phaseolus vulgaris* to induce weight loss without adverse effects (Poddar et al. 2011). However, the major drawback of human studies is that the information about the bioavailability, duration, and dose (safety) of these compounds are different among the reported studies thus remaining still elusive (Venkatakrishnan, Chiu, and Wang 2019). It is noteworthy that the results from human studies on obesity after dietary polyphenols administration are inconsistent about their anti-obesity effects. For example, contradictory results were reported by a recent review analyzing human studies that investigate polyphenols anti-diabetic effect; while some clinical studies correlated the uptake of anthocyanidins and flavan-3-ols to a reduced T2D risk, others do not (Cao et al. 2019). In general, the inconsistency of human studies on obesity could be ascribed to multiple reasons. First of all, the health effects of polyphenols depend on the amount consumed and their bioavailability (Castro-Barquero et al. 2018). It was noted that polyphenols have a low level of oral bioavailability in humans and they are quickly metabolized by tissue enzymes, especially hepatic enzymes, and by gut microbiota (Marin et al. 2015). As a result, the circulating concentrations of free polyphenols in humans are even lower (Baur and Sinclair 2006). Furthermore, the bioavailability of polyphenols in humans can also be modulated by the effects of methods used for food's cooking, processing and storage or by the alteration of phase I/II metabolism by pharmacological or dietary agents (Castro-Barquero et al. 2018). Another reason for the inconclusive clinical outcome

Table 2. Clinical trials on obesity using dietary polyphenols from *clinicaltrials.gov*.

Obesity in adults

Trial Identifier	Trial Phase (status)	Condition or Disease	Intervention	Dose Regimen/Polyphenols Forms/ Study Duration	Primary Outcomes	Results
Completed trials						
NCT04016337	Completed	Obesity Inflammation Insulin Sensitivity	Dietary Supplement: Beverages.	Drink made with lemon and maqui extracts and sweetened with sucralose or saccharose or stevia. 330 mL/day for 60 days	Changes in markers of inflammation, lipid and glycemic metabolism, hormone response, anthropometric parameters and insulin resistance	–
NCT03071718	Completed	Overweight Obesity	Dietary regimen: MED diet Other: Control Diet	Subjects will follow a control diet for 8 weeks	Changes in fasting plasma lipids, in fecal levels of short chain fatty acids	–
NCT03523403	Completed	Obesity Abdominal Hyperlipidemias Inflammation Dysbiosis	Dietary Supplement: HFM with apples Control: HFM	Acute phase: 3 whole apples within 30 minutes Chronic phase: 3 whole apples/day for 6 weeks	Plasma triglyceride levels, plasma inflammatory cytokine levels, gut microbiota profile	–
NCT02333461	Completed	Overweight Obesity	Dietary Supplement: Placebo Dietary Supplement: Apple Dietary Supplement: Grape Dietary Supplement: Raspberry Dietary Supplement: Apricot/Nectarine	333 mg capsule comprised each extract. Consumed as six capsules once daily (total of 2 g/day) with the morning meal for 7 days. HFM was administered at day 1 and 7 of treatment	Serum triglyceride response, Plasma acylated ghrelin response	Only grape extract attenuates hypertriglyceridemia after the consume of a HFM in part by the inhibition of intestinal DGAT1 enzyme activity without intolerable side effects
NCT00692731	Completed	Overweight Obesity	Dietary Supplement: Tea catechin sport beverage Control: Control beverage	Beverage providing approximately 625 mg catechins. Control beverage matched for energy and caffeine content. 500 mL/day for 12 weeks.	Changes in body fat mass.	Tea catechins supplement reduced HFD-induced body weight gain, visceral and liver fat accumulation, and the development of hyperinsulinemia and hyperleptinemia. This supplement also had thermogenic properties and contributed to a decrease in cardiovascular disease risks.
NCT02228291	Completed	Obesity Overweight	Dietary Supplement: Capsule containing citrus flavonoid Dietary Supplement: Placebo	Hesperidin 2S (450 mg/day) or placebo for 6 weeks	Endothelial function.	Consumption of hesperidin 2S improved endothelial dysfunction after a HFM and reduced adhesion molecules only in subjects with baseline FMD $\geq$3%.
NCT02180022	Completed	Healthy Overweight Obese	Drug: Placebo Drug: Onion peel extract	Treatment for 12 weeks	Endothelial function.	–
NCT01674231	Completed	Obesity Inflammation Cardiovascular Disease Oxidative Stress	Dietary Supplement: Grape in the form of freeze-dried whole grape powder Other: Grape powder placebo	Freeze-dried whole GP with 296 mg polyphenols or control food followed by HFHC. 60 g/day for 4 weeks	Decrease inflammatory markers, oxidative stress, increase endothelial function, improve lipid profile, decrease in mononuclear cell production	GP consumption resulted in decreased vasoconstrictor ET-1 concentration and increased expression of genes related to oxidative stress defense following HFHC meal
NCT02006394	Completed	Insulin Resistance Obesity Metabolic Syndrome	Dietary Supplements: Fish oil, polyphenol capsules, corn oil capsules, Corn starch capsules. Other: Reduced glycemic index	Fish oil capsules, delphinidin polyphenol capsules, corn oil capsules, maltodextrin capsules,	Change in insulin resistance	–

			bread products, market variety bread products	made by Zone Labs, placebo bread products, respectively		
NCT03020186	Completed	Abdominal Obesity Metabolic Syndrome	Other: Physical activity Other: Physical activity + MED diet Other: Physical activity + green MED diet	MED diet (+28 walnuts/day). Green-MED diet (+28 g walnuts/day) and green tea (800 mL/day) and Mankai plant (100 g frozen cubes of as a 500-mL green shake)	Abdominal and hepatic fat, obesity	A Green-MED Diet, supplemented with Mankai duckweed, preserved iron-homeostasis in humans.
NCT03203915	Completed	Dyslipidemia Obesity	Dietary Supplement: Chardonnay grape pomace powder high polyphenol dose Dietary Supplement: Chardonnay grape pomace powder low polyphenol dose Dietary Supplement: Placebo	High polyphenol dose: 120 mg, low polyphenol dose: 75 mg. 3 prepackaged capsules taken once in the morning with meal for 3 weeks for each dietary supplement	Change in lipid profile	–
NCT01568827	Completed	Overweight Obese	Dietary Supplement: BRB	Treatment +/– 45 g/day of lyophilized BRBs for 4 days followed by a HFHC	Serum IL-6	Supplement of lyophilized BRB attenuated inflammation in overweight or obese males consuming a HFHC meal
NCT01290250	Completed	Overweight Obesity	Dietary Supplement: OJ based beverage with HPJ or NPJ polyphenols concentration	HPJ: 582.5 mg hesperidin, 125 mg narirutin, and 34 mg didymin. NPJ: 237 mg hesperidin, 45 mg narirutin, and 17 mg didymin. Treatment: 2 daily doses (250 ml each) for 12 weeks	Fasting plasma insulin concentration, fasting plasma triacylglycerols concentration, fasting plasma high-density lipoprotein cholesterol concentration, fasting plasma glucose concentrations, insulin resistance using HOMA, systolic blood pressure, diastolic blood pressure	The consumption of OJ with at least 300 mg flavanones protected against DNA damage and lipid peroxidation, reduced body weight, enhanced the antioxidant defense system (for HPJ), and reduced blood pressure (for LPJ) in overweight and obese adults.
NCT03101436	Completed	Obesity	Dietary Supplement: Extra Virgin Olive Oil and Red Wine	Phase 1: EVOO (80 gr) for 4 weeks. Part 2: red wine (270 ml/day) for 4 weeks	Microbiota Changes	–
NCT01302639	Completed	Obesity, Insulin Sensitivity, Type 2 Diabetes Mellitus	Dietary Supplement: EGCG, resveratol and genistein	- EGCG (282 mg/day) and resveratrol (200 mg/day) +/– genistein (80 mg/day) - placebo. Twice daily (at breakfast and dinner) for a period of 3 days	Postprandial fat oxidation	Short-term supplement of EGCG + RSV increased energy expenditure and altered substrate metabolism in overweight male subjects. Addition of genistein partially reversed these effects possibly due to its higher lipolytic potential
NCT01518764	Completed	Obesity	Dietary Supplement: Red Wine Polyphenols. Dietary Supplement: placebo	RWPs/placebo: 600 mg/day (capsules) for 8 weeks	Insulin sensitivity as determined by euglycemic clamp tests	Supplement of RWPs for 8 weeks did not improve insulin sensitivity in obese patients
NCT03423719	Completed	Overweight Obese	Dietary Supplement: Fiit-ns® Dietary Supplement: Placebo	Fiit-ns®: blend of polyphenol-rich extracts from grapefruit, grape, green tea, guarana and black carrot, vitamin B3. Daily dosage: 900 mg in (two capsules of 450 mg) for 16 weeks	Change in health-related quality of life as assessed by the SF-36 Health Survey	–
NCT04153617	Completed	Overweight and Obesity Dyslipidemias	Dietary Supplement: Control honey Dietary Supplement: Modified honey	Control honey: orange blossom honey. Modified honey: with soluble fiber and polyphenols.	Change from baseline satiety hunger assessment	–

(*continued*)

Table 2. Continued.

Obesity in adults

Trial Identifier	Trial Phase (status)	Condition or Disease	Intervention	Dose Regimen/Polyphenols Forms/ Study Duration	Primary Outcomes	Results
				Middle term trial: 40 g/day for 3 months in two daily intakes of 20 g/day. Short term trial: 20 g/day in a single day		
NCT02710461	Completed	Subjects With Abdominal Obesity	Dietary Supplement: Mixture of grape pomace and pomegranate pomace	–	Postprandial glucose	–
Underway trials						
NCT02167555	Active, not recruiting	Overweight Obese Healthy	Dietary Supplement: Active Comparator Dietary Supplement: Placebo Comparator	Active Comparator: WBB. Placebo Comparator: Placebo Beverage	Changes in plasma and urine polyphenol metabolite concentrations over 24 hours after WBB consumption with a HFHC meal	Data indicated bioavailability of early and late phase WBB metabolites peaking at different times during the 24h period
NCT02949115	Active, not recruiting	Overweight Obesity Aging Menopause	Dietary Supplement: red beetroot juice Dietary Supplement: red beetroot juice without nitrate Dietary Supplement: placebo drink plus potassium nitrate Dietary Supplement: placebo drink	Intake of 70 mL/day for each dietary supplement followed by a HFM. Placebo drink plus potassium nitrate: 489 mg potassium nitrate (300 mg nitrate)	Vascular endothelial function	RBJ exposure did not alter postprandial endothelial function or other outcomes despite increasing NOx concentrations
NCT02167607	Active, not recruiting	Premenopausal Women Overweight and Obese Women	Dietary Supplement: Active Comparator Dietary Supplement: Placebo Comparator	Active Comparator: Purple Potato. Placebo Comparator: White Potato	Changes in plasma polyphenol metabolite concentrations over 6 hours after white or purple potato consumption with a HFHC meal	–
NCT03741218	Completed	Obesity	Other: Freeze-dried grape (GRAP)/ Placebo (PLA)	GRAP: monodose of freeze-dried grapes (equivalent to 300 g of fresh grapes). All subjects received a HF breakfast and a medium-fat lunch twice. Experimental 1: breakfast + PLA the first time and + GRAP the second time. Experimental 2: same treatment, opposite order.	Postprandial glucose (300-420 min)	–
NCT04100200	Recruiting	Overweight or Obesity Healthy	Dietary Supplement: Mixed berries Dietary Supplement: FOS Dietary Supplement: Control Dietary Supplement: Combination	4 weeks of treatment: strawberry and red raspberry, fructo-oligosaccharide, placebo similar in color to mixed berry supplement without any polyphenols, mixed berry composite + FOS	Changes in plasma biomarkers and measures of inflammation concentration: Nrf2/NF-κB, inflammatory cytokines and GLP-2. Response between 4 treatments for all the outcomes.	–
NCT04149288	Not yet recruiting	Healthy Normal Weight Overweight Obese	Dietary Supplement: High-polyphenol olive oil Dietary Supplement: Low-polyphenol olive oil	40 mL/day for 2 weeks	Assessing the influence of olive oil polyphenols on: cholesterol efflux, CETP, circulating oxidized LDL, blood lipid measurements, on PON-1 activity, PBMCs	–

					using *ex vivo* stimulation assays	
NCT04190706	Not yet recruiting	Cardiometabolic Risk Abdominal Obesity	Other: bioactive components fortified food products intake (biscuits and cookies) Other: control food products intake (biscuits and cookies)	100 g/day of fortified or standard biscuits and cookies for 9 weeks. Last week: daily consumption of a fructose solution (3 g/kg fat free mass)	Change from baseline postprandial plasma endotoxemia binding protein kinetics: LBP and CD14	–
Obesity in childhood						
Trial Identifier	**Trial Phase (status)**	**Condition or Disease**	**Intervention**	**Dose Regimen/ Polyphenols Forms/ Study Duration**	**Primary Outcome**	**Results**
Completed trials						
NCT01705093	Completed	Childhood Obesity Cardiovascular Disease	Dietary Supplement: Experimental: flavonoid-rich freeze-dried strawberry powder. Placebo: macronutrient-matched control powder	50 g of flavonoid-rich freeze-dried strawberry or macronutrient-matched control powder for 1 week	Vascular function measured by peripheral arterial tonometry	–
Underway trials						
NCT03628937	Active, not recruiting	Pediatric Obesity, Puberty, Precocious	Dietary Supplement: Decaffeinated Green Tea Polyphenol Other: Placebo control	Decaffeinated green tea polyphenol: EGCG accounted for 50%. 400 mg/capsule. 1 capsule/day after breakfast for 12 weeks	The incidence of precocious puberty in the intervention groups and the placebo group	
NCT03994029	Not yet recruiting	Obesity, Childhood Hepatic Steatosis Intimal Hyperplasia	Dietary Supplement: Polyphenol supplementation Other: Placebo control	120 mg/day of powder polyphenol for 60 days. Placebo: 1 tab PO QD/day for 60 days	Change in hepatic steatosis MR, change in hepatic steatosis US shear wave elastography, change in hepatic steatosis B-mode US	
NCT04112251	Not yet recruiting	Childhood Obesity Adolescent Obesity	Dietary Supplement: Cocoa Flavonols Supplement. Other: placebo	Cocoa flavonoids: 500 mg capsule (100 mg/day of epicatechin) every 12 hours for 12 weeks. Placebo: 500 mg oral placebo capsule (Cornstarch) every 12 hours for 12 weeks	TG/HDL-C ratio, BFM percentage, Insulin Resistance Homeostasis Evaluation Model (HOMA-IR)	Administration of epicatechin induced favorable effects on glycemia homeostasis, lipid profile and systemic inflammation

Abbreviations: body fat mass (BFM), Black raspberry Slurry (BRB), cholesterol ester transfer protein activity (CETP), Cluster of differentiation 14 (CD14), diacylglycerol acyltransferase 1 (DGAT1), endothelin 1 (ET-1), epigallocatechin gallate (EGCG), extra virgin olive oil (EVOO), flow-mediated dilation (FMD), fructo-oligosaccharide (FOS), glucagon like peptide 2 (GLP-2), grape powder (GP), high fat diet (HFD), high fat high carbohydrate (HFHC), high-fat meal (HFM), high polyphenols concentration in beverage (HPJ), lipopolysaccharide-binding protein (LBP), Mediterranean diet (MED diet), nitrate/nitrite (NOx), normal polyphenols concentration in beverage (NPJ), orange juice (OJ), peripheral blood mononuclear cells (PBMCs), paraoxinase-1 (PON-1), red beetroot juice (RBJ), red wine polyphenols (RWPs), resveratrol (RSV), triglyceride/high-density lipoprotein cholesterol (TG/HDL-C), wild blueberry beverage (WBB).

of anti-obesity human studies using dietary polyphenols is the different study designs and lengths, and the variation among subjects in terms of age, gender and ethnicity. In fact, the high heterogeneity found in the individual responses to nutrients could be explained by the genetic background and by differences in the polyphenol intake due to the dietary regimen consumed within countries as for Western diet with a low intake of polyphenols in industrialized countries (Burkholder-Cooley et al. 2016). Also, measurement errors in dietary intake could be responsible for inconsistency of the results in human studies (Chiva-Blanch and Badimon 2017). These errors could both rely on the analytical method used to quantify polyphenols in foods (e.g. Folin-Ciocalteu colorimetric assay versus chromatographic techniques) and on the approach used to determine polyphenol intake in humans (Spencer et al. 2008). For the latter, there are two ways of action; determine biomarkers of intake by the same techniques cited before or estimate its intake. The estimation of polyphenols intake is performed by administering food frequency questionnaires or food recalls to the study participants and by using databases to translate this information to single or total polyphenols (Pinto and Santos 2017). The drawback of this approach is the self-reporting bias and the fact that it does not considered variations in the polyphenolic composition of foods due to the seasonal and geographical variability, the ripeness of the food at time of harvest and its storage before consumption, and the limited data on the polyphenolic composition reported on food databases (Pinto and Santos 2017).

Moreover, most of the human studies testing polyphenols' anti-obesity impact did not consider the synergistic effect of different polyphenols' classes and of a specific class of polyphenols with other dietary compounds. In fact, as for in vitro, in vivo and ex vivo experiments, human studies are mainly focused on the evaluation of single polyphenols' effects without considering that multiple types of polyphenols are present in the whole foods and that different types of phytochemicals are typically consumed simultaneously from various food sources (Fraga et al. 2019). In this scenario, in human studies it could be better to use food extract instead of a single polyphenol compound.

As reported in Table 2, the number of clinical trials on childhood obesity using dietary polyphenols is very limited until now and, more importantly, most of them are at a very early status. The only one completed study is focused on the evaluation of the association between childhood obesity and cardiovascular disease, even if no date is reported until now (Table 2). This underlines that the recent clinical research, in line with the strategies adopted by the EU, is trying to respond to the need of halting the rise of obesity in children. The paucity of human studies on childhood obesity is possibly due to the severity to obtain ethical approval and to the limited amount of biological samples. Moreover, clinical research involving infants, children, and adolescents is more challenging than research involving adults. The challenges include the need for developing appropriate outcome measures for children of different ages, the complexities of parental involvement and family decision making, and the adaptations required in research procedures and settings to accommodate children's physical, cognitive, and emotional development. Understanding and complying with the special ethical and regulatory protections for children constitutes another challenge. These various challenges underscore the need for those reviewing research protocols that include children to have adequate expertise in different areas of child health and research. Anyway, a great advantage of nutritional studies conducted on children is the higher compliance relative to those on adult patients thanks to the ability to control alimentary patterns thus limiting the confounding factors commonly found in the human diet.

Finally, a critical issue to be considered in clinical studies is the risk associated with a high consumption of polyphenols. In fact, based on the dose used, some polyphenols could become pro-inflammatory and pro-oxidant; pro-oxidant activity could be mediated by the phenoxyl radicals of dietary polyphenols (Han, Shen, and Lou 2007). In general, a high dose of polyphenols could be correlated with carcinogenic/genotoxic effects, the interfering with thyroid hormone biosynthesis, and the interaction with certain pharmaceutical agents (Mennen et al. 2005). It is important to note that a high polyphenols dose correlating to the side effects depends on the concentration at which these compounds occur in the diet and the effective dose able to reach the target site.

The translation of data from preclinical to clinical studies, normally correlates with a lower dose used in human setting than in the preclinical one. In fact, the concentrations of plasma metabolites after a normal dietary intake rarely exceed nmol/L, while the in vitro concentrations tested for polyphenols normally range from μmol/L to mmol/L (Visioli et al. 2011). The lower dose of polyphenols in humans could be the reason why the risk associated with high polyphenol intake is in general quite low (Mennen et al. 2005). Importantly, as reported before, the low dose of polyphenols in human settings could be explained by issues linked to bioavailability in humans that could support the inconsistency of data obtained from clinical studies relative to those obtained from the preclinical ones (Chiva-Blanch and Badimon 2017). In fact, the benefic effects of polyphenols both rely on their intake and bioavailability (D'Archivio et al. 2007). The latter is influenced by different sequential variables; intestinal absorption (direct process for aglycones), metabolism by the microbiota, intestinal and hepatic metabolism (collectively regulating the indirect adsorption process for esters, glycosides, or polymers), nature of circulating metabolites and their binding to serum transporters (mainly albumin), cellular uptake, tissues accumulation, and biliary and urinary excretion (Renaud and Martinoli 2019). It is important to note that the huge variability of the resulting metabolites, apart from all these mechanisms, also rely on the individual composition of the gut microbiota as wells as on the individual genetic variations of the enzymes involved in polyphenols metabolism (Aragonès et al. 2017). Moreover, bioavailability greatly differs among polyphenols and, for some of them, among dietary sources, depending on the food matrix (Schilter et al. 2003). This is the reason why the most abundant polyphenol types in a specific diet

did not correlate with the highest concentrations of active metabolites found in the target tissues. To study the differences in bioavailability of different polyphenols classes, a correlation of quantities contained in food sources, plasma concentration, half-lives and excretion data should be done, even possible. In general, plasma concentration of metabolites peaks at 2–4 h after polyphenols ingestion and falls to baseline levels within 8–12 hours (D'Archivio et al. 2007). However, some differences among polyphenols types exist (Kang et al. 2019). The analysis of these data could also explain contrasting results obtained from human studies due to the wrong timing choose for the analysis to evaluate polyphenols effects. Moreover, these data could help to choose the right duration of the study suggesting a long term intervention studies in the case of polyphenols that are rapidly absorbed and excreted.

Furthermore, data from 97 human studies were investigated to evaluate the kinetics and the extent of polyphenol absorption after ingestion of a single dose of polyphenol provided as pure compound, plant extract, or whole food/beverage (Manach et al. 2005). The plasma concentrations of total metabolites ranged from 0 to 4 μmol/L with an intake of 50 mg aglycone equivalents, and the relative urinary excretion ranged from 0.3% to 43% of the ingested dose depending on the polyphenol tested. The polyphenols that are most well absorbed in humans are isoflavones and gallic acid, followed by catechins, flavanones, and quercetin glucosides characterized by different kinetics. On the contrary, proanthocyanidins, the galloylated tea catechins, and the anthocyanins are the least well absorbed polyphenols.

Considering all the variables influencing the bioavailability, the polyphenols forms reaching the blood and tissues are different from those present in food or plant of origin; this could differently modulates the biological properties of polyphenols (Cory et al. 2018). Regrettably, most of the published in vitro studies investigating mechanisms of action of polyphenols, do not take into account all these processes and used the native form of polyphenols found in foods or plant extracts (thus high doses) generating data with limited utility in terms of translational research (Ottaviani et al. 2016). To fill this gap, considering the extensive metabolism of polyphenols in vivo, it could be better to start with the study of their bioavailability and then test the resulting metabolites, instead of the native compounds, in ex vivo and in vitro models (Ottaviani et al. 2016). Data obtained by this strategy could help in the identification of the active components to which the health effects of polyphenols are ascribed to, with the indication for the effective dose thanks to a correct evaluation of the real polyphenol intake (Ottaviani et al. 2016). More importantly, these data could guide researchers in the design and the execution of more rigorous dietary intervention studies that will also take into account important concerns about safety and risks associated with polyphenols intake in humans.

All the considerations given for the studies on adult obese patients could be taken into account in the study design of future clinical trials investigating the benefic effects of polyphenols in childhood obesity.

The state-of-art on nutrigenomics induced by dietary polyphenols on overweight or obese patients discussed in this section, clearly indicates that this is mainly an unexplored area thus underling the need for more research on these theme. A key point of these new research should be the correlation between the transcriptional modulation induced by dietary polyphenols and the metabolic changes observed in the context of obesity. This need become more urgent for childhood obesity; in this case, to avoid issue related to side effects induced by a high polyphenol dose it could be better to use functional foods according to the Recommended daily allowance (RDA) instead of nutraceuticals.

5. Conclusion

Despite the rapid increase in prevalence of obesity in the last decades, a favorable aspect to be considered is that it is a preventable disease. A multisector approach with the promotion of a healthier lifestyle in terms of nutrition and physical activity is needed. Specifically, the use of dietary regimen rich in anti-inflammatory nutrients, like polyphenols, could be considered as a promising preventive and therapeutic approach for obesity. Several studies on cell culture, animal and human models provide strong evidence on polyphenols' anti-oxidant and anti-inflammatory abilities with a positive effect also on thermogenesis and energy expenditure facilitating weight loss, by acting at molecular level. Anyway, the number of human studies investigating dietary polyphenols' ability to modulate the transcriptome is still limited and the reported results are controversial relative to what observed in preclinical studies. The discussion on the critical issues reported in this review to fill the gap between preclinical and clinical studies will assist researchers to obtain more reliable data. This could help responding to the urgent need for more clinical studies on obese patients, especially on children, to investigate the anti-obesity effects of dietary polyphenols in preventive and/or therapeutic approaches to fight obesity.

Acknowledgements

EU project 820587—OLIVE-SOUND—Ultrasound reactor—The solution for a continuous olive oil extraction process H2020-EU.2.1—INDUSTRIAL LEADERSHIP—EIC-FTI-2018–2020—Fast Track to Innovation (FTI)—European Union's Horizon 2020 research and innovation program under grant agreement No. 820587.

Disclosure Statement

The authors declare no conflict of interest.

Funding

Stefania De Santis is funded by PON -Ricerca e Innovazione 2014-2020-: Progetto AIM1801289—attività 3—linea 1.

ORCID

De Santis Stefania http://orcid.org/0000-0001-6877-2208
M. L. Clodoveo http://orcid.org/0000-0002-1717-2197
M. Cariello http://orcid.org/0000-0002-7537-6657
C. Franchini http://orcid.org/0000-0002-3725-750X
M. F. Faienza http://orcid.org/0000-0002-1899-8337
F. Corbo http://orcid.org/0000-0002-6951-1103

References

Agostini, M., E. Schoenmakers, C. Mitchell, I. Szatmari, D. Savage, A. Smith, O. Rajanayagam, R. Semple, J. Luan, L. Bath, et al. 2006. Non-DNA binding, dominant-negative, human PPARgamma mutations cause lipodystrophic insulin resistance. *Cell Metabolism* 4 (4): 303–11. doi: 10.1016/j.cmet.2006.09.003.

Aguirre, L., A. Fernandez-Quintela, N. Arias, and M. P. Portillo. 2014. Resveratrol: Anti-obesity mechanisms of action. *Molecules (Basel, Switzerland)* 19 (11):18632–55. doi: 10.3390/molecules191118632.

Ahn, J., H. Lee, S. Kim, and T. Ha. 2010. Curcumin-induced suppression of adipogenic differentiation is accompanied by activation of Wnt/beta-catenin signaling. *American Journal of Physiology. Cell Physiology* 298 (6):C1510–6. doi: 10.1152/ajpcell.00369.2009.

Alberdi, G., V. M. Rodriguez, J. Miranda, M. T. Macarulla, N. Arias, C. Andres-Lacueva, and M. P. Portillo. 2011. Changes in white adipose tissue metabolism induced by resveratrol in rats. *Nutrition & Metabolism* 8 (1):29doi: 10.1186/1743-7075-8-29.

Andrade, J. M., A. C. Frade, J. B. Guimaraes, K. M. Freitas, M. T. Lopes, A. L. Guimaraes, A. M. de Paula, C. C. Coimbra, and S. H. Santos. 2014. Resveratrol increases brown adipose tissue thermogenesis markers by increasing SIRT1 and energy expenditure and decreasing fat accumulation in adipose tissue of mice fed a standard diet. *European Journal of Nutrition* 53 (7):1503–10. doi: 10.1007/s00394-014-0655-6.

Andrade, J. M. O., A. S. Barcala-Jorge, G. C. Batista-Jorge, A. F. Paraíso, K. M. d Freitas, D. d F. Lelis, A. L. S. Guimarães, A. M. B. de Paula, and S. H. S. Santos. 2019. Effect of resveratrol on expression of genes involved thermogenesis in mice and humans. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 112:108634doi: 10.1016/j.biopha.2019.108634.

Anhe, F. F., T. V. Varin, M. L. Barz, Y. Desjardins, E. Levy, D. Roy, and A. Marette. 2015. Gut microbiota dysbiosis in obesity-linked metabolic diseases and prebiotic potential of polyphenol-rich extracts. *Current Obesity Reports* 4 (4):389–400. doi: 10.1007/s13679-015-0172-9.

Aragonès, G., F. Danesi, D. Del Rio, and P. Mena. 2017. The importance of studying cell metabolism when testing the bioactivity of phenolic compounds. *Trends in Food Science & Technology the Technology* 69:230–42. doi: 10.1016/j.tifs.2017.02.001.

Barathikannan, K., R. Chelliah, M. Rubab, E. B. Daliri, F. Elahi, D. H. Kim, P. Agastian, S. Y. Oh, and D. H. Oh. 2019. Gut microbiome modulation based on probiotic application for anti-obesity: A review on efficacy and validation. *Microorganisms Gut Microorganisms* 7 (10):456. doi: 10.3390/microorganisms7100456.

Barbera, M. J., A. Schluter, N. Pedraza, R. Iglesias, F. Villarroya, and M. Giralt. 2001. Peroxisome proliferator-activated receptor alpha activates transcription of the brown fat uncoupling protein-1 gene. A link between regulation of the thermogenic and lipid oxidation pathways in the brown fat cell. *The Journal of Biological Chemistry* 276 (2):1486–93. doi: 10.1074/jbc.M006246200.

Barrera-Reyes, P. K., N. Hernandez-Ramirez, J. Cortes, L. Poquet, K. Redeuil, C. Rangel-Escareno, M. Kussmann, I. Silva-Zolezzi, and M. E. Tejero. 2019. Gene expression changes by high-polyphenols cocoa powder intake: A randomized crossover clinical study. *European Journal of Nutrition* 58 (5):1887–98. doi: 10.1007/s00394-018-1736-8.

Baur, J. A., and D. A. Sinclair. 2006. Therapeutic potential of resveratrol: The in vivo evidence. *Nature Reviews. Drug Discovery* 5 (6): 493–506. doi: 10.1038/nrd2060.

Baur, J. A., D. Chen, E. N. Chini, K. Chua, H. Y. Cohen, R. de Cabo, C. Deng, S. Dimmeler, D. Gius, L. P. Guarente, et al. 2010. Dietary restriction: Standing up for sirtuins. *Science (New York, N.Y.)* 329 (5995):1012–3. author reply 1013-4. doi: 10.1126/science.329.5995.1012.

Bleich, S. N., J. Jones-Smith, J. A. Wolfson, X. Zhu, and M. Story. 2015. The complex relationship between diet and health. *Health Affairs (Project Hope)* 34 (11):1813–20. doi: 10.1377/hlthaff.2015.0606.

Bo, S., M. Fadda, D. Fedele, M. Pellegrini, E. Ghigo, and N. Pellegrini. 2020. A Critical Review on the Role of Food and Nutrition in the Energy Balance. *Nutrients* 12 (4):1161. doi: 10.3390/nu12041161.

Bost, F., M. Aouadi, L. Caron, and B. Binetruy. 2005. The role of MAPKs in adipocyte differentiation and obesity. *Biochimie*87 (1): 51–6. doi: 10.1016/j.biochi.2004.10.018.

Bracale, R., M. L. Petroni, S. Davinelli, U. Bracale, G. Scapagnini, M. O. Carruba, and E. Nisoli. 2014. Muscle uncoupling protein 3 expression is unchanged by chronic ephedrine/caffeine treatment: Results of a double blind, randomised clinical trial in morbidly obese females. *PLoS One* 9 (6):e98244. doi: 10.1371/journal.pone.0098244.

Burcelin, R. 2016. Gut microbiota and immune crosstalk in metabolic disease. *Molecular Metabolism* 5 (9):771–81. doi: 10.1016/j.molmet.2016.05.016.

Burkholder-Cooley, N., S. Rajaram, E. Haddad, G. E. Fraser, and K. Jaceldo-Siegl. 2016. Comparison of polyphenol intakes according to distinct dietary patterns and food sources in the Adventist Health Study-2 cohort. *The British Journal of Nutrition* 115 (12):2162–9. doi: 10.1017/S0007114516001331.

Cai, S., W. Sun, Y. Fan, X. Guo, G. Xu, T. Xu, Y. Hou, B. Zhao, X. Feng, and T. Liu. 2016. Effect of mulberry leaf (Folium Mori) on insulin resistance via IRS-1/PI3K/Glut-4 signalling pathway in type 2 diabetes mellitus rats. *Pharmaceutical Biology* 54 (11):2685–91. doi: 10.1080/13880209.2016.1178779.

Camargo, A., J. Ruano, J. M. Fernandez, L. D. Parnell, A. Jimenez, M. Santos-Gonzalez, C. Marin, P. Perez-Martinez, M. Uceda, J. Lopez-Miranda, et al. 2010. Gene expression changes in mononuclear cells in patients with metabolic syndrome after acute intake of phenol-rich virgin olive oil. *BMC Genomics*11:253doi: 10.1186/1471-2164-11-253.

Camargo, A., O. A. Rangel-Zuniga, C. Haro, E. R. Meza-Miranda, P. Pena-Orihuela, M. E. Meneses, C. Marin, E. M. Yubero-Serrano, P. Perez-Martinez, J. Delgado-Lista, et al. 2014. Olive oil phenolic compounds decrease the postprandial inflammatory response by reducing postprandial plasma lipopolysaccharide levels. *Food Chemistry* 162:161–71. doi: 10.1016/j.foodchem.2014.04.047.

Canto, C.,. Z. Gerhart-Hines, J. N. Feige, M. Lagouge, L. Noriega, J. C. Milne, P. J. Elliott, P. Puigserver, and J. Auwerx. 2009. AMPK regulates energy expenditure by modulating NAD + metabolism and SIRT1 activity. *Nature*458 (7241):1056–60. doi: 10.1038/nature07813.

Cao, H., J. Ou, L. Chen, Y. Zhang, T. Szkudelski, D. Delmas, M. Daglia, and J. Xiao. 2019. Dietary polyphenols and type 2 diabetes: Human study and clinical trial. *Critical Reviews in Food Science and Nutrition* 59 (20):3371–9. doi: 10.1080/10408398.2018.1492900.

Carpi, S., E. Scoditti, M. Massaro, B. Polini, C. Manera, M. Digiacomo, J. E. Salsano, G. Poli, T. Tuccinardi, S. Doccini, et al. 2019. The extra-virgin olive oil polyphenols oleocanthal and oleacein counteract inflammation-related gene and miRNA expression in adipocytes by attenuating NF-kappaB activation. *Nutrients*11 (12):2855. doi: 10.3390/nu11122855.

Castro-Barquero, S., R. M. Lamuela-Raventos, M. Domenech, and R. Estruch. 2018. Relationship between Mediterranean dietary polyphenol intake and obesity. *Nutrients Relationship Nutrients* 10 (10): 1523. doi: 10.3390/nu10101523.

Chan, C. Y., L. Wei, F. Castro-Munozledo, and W. L. Koo. 2011. (−)-Epigallocatechin-3-gallate blocks 3T3-L1 adipose conversion by inhibition of cell proliferation and suppression of adipose phenotype expression. *Life Sciences* 89 (21–22):779–85. doi: 10.1016/j.lfs.2011.09.006.

Chen, N., R. Bezzina, E. Hinch, P. A. Lewandowski, D. Cameron-Smith, M. L. Mathai, M. Jois, A. J. Sinclair, D. P. Begg, J. D. Wark, et al. 2009. Green tea, black tea, and epigallocatechin modify body composition, improve glucose tolerance, and differentially alter metabolic gene expression in rats fed a high-fat diet. *Nutrition Research* 29 (11):784–93. doi: 10.1016/j.nutres.2009.10.003.

Chen, S., Z. Li, W. Li, Z. Shan, and W. Zhu. 2011. Resveratrol inhibits cell differentiation in 3T3-L1 adipocytes via activation of AMPK. *Canadian Journal of Physiology and Pharmacology* 89 (11):793–9. doi: 10.1139/y11-077.

Chen, S., X. Xiao, X. Feng, W. Li, N. Zhou, L. Zheng, Y. Sun, Z. Zhang, and W. Zhu. 2012. Resveratrol induces Sirt1-dependent apoptosis in 3T3-L1 preadipocytes by activating AMPK and suppressing AKT activity and survivin expression. *The Journal of Nutritional Biochemistry* 23 (9):1100–12. doi: 10.1016/j.jnutbio.2011.06.003.

Chiva-Blanch, G., and L. Badimon. 2017. Effects of polyphenol intake on metabolic syndrome: Current evidences from human trials. *Oxidative Medicine and Cellular Longevity* 2017:5812401doi: 10.1155/2017/5812401.

Cho, S. Y., P. J. Park, H. J. Shin, Y. K. Kim, D. W. Shin, E. S. Shin, H. H. Lee, B. G. Lee, J. H. Baik, and T. R. Lee. 2007. (–)-Catechin suppresses expression of Kruppel-like factor 7 and increases expression and secretion of adiponectin protein in 3T3-L1 cells. *American Journal of Physiology. Endocrinology and Metabolism* 292 (4): E1166–72. doi: 10.1152/ajpendo.00436.2006.

Chung, J. H., V. Manganiello, and J. R. Dyck. 2012. Resveratrol as a calorie restriction mimetic: Therapeutic implications. *Trends in Cell Biology* 22 (10):546–54. doi: 10.1016/j.tcb.2012.07.004.

Ciccone, M. M., M. F. Faienza, M. Altomare, C. Nacci, M. Montagnani, F. Valente, F. Cortese, M. Gesualdo, A. Zito, R. Mancarella, et al. 2016. Endothelial and metabolic function interactions in overweight/obese children. *Journal of Atherosclerosis and Thrombosis* 23 (8):950–9. doi: 10.5551/jat.31740.

Collaborators G. B. D. D. 2019. Health effects of dietary risks in 195 countries, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 393:1958–72.

Corbo, F., G. Brunetti, P. Crupi, S. Bortolotti, G. Storlino, L. Piacente, A. Carocci, A. Catalano, G. Milani, G. Colaianni, et al. 2019. Effects of sweet cherry polyphenols on enhanced osteoclastogenesis associated with childhood obesity. *Front Immunology* 10:1001.

Cory, H., S. Passarelli, J. Szeto, M. Tamez, and J. Mattei. 2018. The role of polyphenols in human health and food systems: A mini-review. *Frontiers in Nutrition* 5:87doi: 10.3389/fnut.2018.00087.

Costa, C. d S., F. Rohden, T. O. Hammes, R. Margis, J. W. Bortolotto, A. V. Padoin, C. C. Mottin, and R. M. Guaragna. 2011. Resveratrol upregulated SIRT1, FOXO1, and adiponectin and downregulated PPARgamma1-3 mRNA expression in human visceral adipocytes. *Obesity Surgery* 21 (3):356–61. doi: 10.1007/s11695-010-0251-7.

Cox, L. M., and M. J. Blaser. 2013. Pathways in microbe-induced obesity. *Cell Metabolism* 17 (6):883–94. doi: 10.1016/j.cmet.2013.05.004.

D'Amore, S., M. Vacca, M. Cariello, G. Graziano, A. D'Orazio, R. Salvia, R. C. Sasso, C. Sabba, G. Palasciano, and A. Moschetta. 2016. Genes and miRNA expression signatures in peripheral blood mononuclear cells in healthy subjects and patients with metabolic syndrome after acute intake of extra virgin olive oil. *Biochimica et Biophysica Acta* 1861 (11):1671–80. doi: 10.1016/j.bbalip.2016.07.003.

D'Archivio, M., C. Filesi, R. Di Benedetto, R. Gargiulo, C. Giovannini, and R. Masella. 2007. Polyphenols, dietary sources and bioavailability. *Ann Ist Super Sanita* 43:348–61.

De Santis, S.,. V. Galleggiante, L. Scandiffio, M. Liso, E. Sommella, A. Sobolewski, V. Spilotro, A. Pinto, P. Campiglia, G. Serino, et al. 2017. Secretory leukoprotease inhibitor (Slpi) expression is required for educating murine dendritic cells inflammatory response following quercetin exposure. *Nutrients* 9 (7):706. doi: 10.3390/nu9070706.

De Santis, S.,. M. Cariello, E. Piccinin, C. Sabba, and A. Moschetta. 2019. Extra virgin olive oil: Lesson from nutrigenomics. *Nutrients*11 (9):2085. doi: 10.3390/nu11092085.

DeFronzo, R. A., E. Ferrannini, L. Groop, R. R. Henry, W. H. Herman, J. J. Holst, F. B. Hu, C. R. Kahn, I. Raz, G. I. Shulman, et al. 2015. Type 2 diabetes mellitus. *Nature Reviews. Disease Primers* 1: 15019doi: 10.1038/nrdp.2015.19.

DeFuria J., G. Bennett, K. J. Strissel, J. W. Perfield, P. E. Milbury, A. S. Greenberg and M. S. Obin. 2009. Dietary blueberry attenuates whole-body insulin resistance in high fat-fed mice by reducing adipocyte death and its inflammatory sequelae. *Journal of Nutrition Dietary blueberry attenuates whole-body insulin resistance in high fat-fed mice by reducing adipocyte death and its inflammatory sequelae* 139:1510–6.

Del Rio, D., A. Rodriguez-Mateos, J. P. Spencer, M. Tognolini, G. Borges, and A. Crozier. 2013. Dietary (poly)phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxidants & Redox Signaling* 18 (14): 1818–92. doi: 10.1089/ars.2012.4581.

Do, G. M., U. J. Jung, H. J. Park, E. Y. Kwon, S. M. Jeon, R. A. McGregor, and M. S. Choi. 2012. Resveratrol ameliorates diabetes-related metabolic changes via activation of AMP-activated protein kinase and its downstream targets in db/db mice. *Molecular Nutrition & Food Research* 56 (8):1282–91. doi: 10.1002/mnfr.201200067.

Donmez, G., and L. Guarente. 2010. Aging and disease: Connections to sirtuins. *Aging Cell Aging Cell* 9 (2):285–90. doi: 10.1111/j.1474-9726.2010.00548.x.

Doo, M., and Y. Kim. 2015. Obesity: Interactions of genome and nutrients intake. *Preventive Nutrition and Food Science* 20 (1):1–7. doi: 10.3746/pnf.2015.20.1.1.

Ducheix, S., C. Peres, J. Hardfeldt, C. Frau, G. Mocciaro, E. Piccinin, J. M. Lobaccaro, S. De Santis, M. Chieppa, J. Bertrand-Michel, et al. 2018. Deletion of stearoyl-CoA desaturase-1 from the intestinal epithelium promotes inflammation and tumorigenesis, reversed by dietary oleate. *Gastroenterology* 155 (5):1524–38 e9. doi: 10.1053/j.gastro.2018.07.032.

Ejaz, A., D. Wu, P. Kwan, and M. Meydani. 2009. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. *The Journal of Nutrition* 139 (5):919–25. doi: 10.3945/jn.108.100966.

EUActionPlan2014. EU Action Plan on Childhood Obesity 2014–2020. *EU Action Plan on Childhood Obesity 2014–2020*

Faienza, M. F., N. Santoro, R. Lauciello, R. Calabro, L. Giordani, G. D. Salvo, A. Ventura, M. Delvecchio, L. Perrone, E. M. Del Giudice, et al. 2010. IGF2 gene variants and risk of hypertension in obese children and adolescents. *Pediatric Research* 67 (4):340–4. doi: 10.1203/PDR.0b013e3181d22757.

Faienza, M. F., R. Francavilla, R. Goffredo, A. Ventura, F. Marzano, G. Panzarino, G. Marinelli, L. Cavallo, and G. D. Bitonto. 2012. Oxidative stress in obesity and metabolic syndrome in children and adolescents. *Hormone Research in Paediatrics* 78 (3):158–64. doi: 10.1159/000342642.

Faienza, M. F., A. Acquafredda, R. Tesse, V. Luce, A. Ventura, N. Maggialetti, M. Monteduro, P. Giordano, and L. Cavallo. 2013. Risk factors for subclinical atherosclerosis in diabetic and obese children. *International Journal of Medical Sciences* 10 (3):338–43. doi: 10.7150/ijms.5181.

Faienza, M. F., D. Q. Wang, G. Fruhbeck, G. Garruti, and P. Portincasa. 2016. The dangerous link between childhood and adulthood predictors of obesity and metabolic syndrome. *Internal and Emergency Medicine* 11 (2):175–82. doi: 10.1007/s11739-015-1382-6.

Faienza, M. F., A. Ventura, M. Delvecchio, A. Fusillo, L. Piacente, G. Aceto, G. Colaianni, S. Colucci, L. Cavallo, M. Grano, et al. 2017. High sclerostin and Dickkopf-1 (DKK-1) serum levels in children and adolescents with Type 1 diabetes mellitus. *Journal of Clinical Endocrinology & Metabolism* 102:1174–81.

Faienza, M. F., G. D'Amato, M. Chiarito, G. Colaianni, S. Colucci, M. Grano, F. Corbo, and G. Brunetti. 2019. Mechanisms involved in childhood obesity-related bone fragility. *Frontiers in Endocrinology* 10:269. doi: 10.3389/fendo.2019.00269.

Faienza, M. F., F. Corbo, A. Carocci, A. Catalano, M. L. Clodoveo, M. Grano, D. Q. H. Wang, G. D'Amato, M. Muraglia, C. Franchini, et al. 2020. Novel insights in health-promoting properties of sweet

cherries. *Journal of Functional Foods*69:103945. doi: 10.1016/j.jff.2020.103945.

Floyd, Z. E., Z. Q. Wang, G. Kilroy, and W. T. Cefalu. 2008. Modulation of peroxisome proliferator-activated receptor gamma stability and transcriptional activity in adipocytes by resveratrol. *Metabolism: Clinical and Experimental* 57 (7 Suppl 1):S32–S8. doi: 10.1016/j.metabol.2008.04.006.

Fraga, C. G., K. D. Croft, D. O. Kennedy, and F. A. Tomas-Barberan. 2019. The effects of polyphenols and other bioactives on human health. *Food & Function* 10 (2):514–28. doi: 10.1039/c8fo01997e.

Frescas, D., L. Valenti, and D. Accili. 2005. Nuclear trapping of the forkhead transcription factor FoxO1 via Sirt-dependent deacetylation promotes expression of glucogenetic genes. *The Journal of Biological Chemistry* 280 (21):20589–95. doi: 10.1074/jbc.M412357200.

Fulco, M., and V. Sartorelli. 2008. Comparing and contrasting the roles of AMPK and SIRT1 in metabolic tissues. *Cell Cycle (Georgetown, Tex.)* 7 (23):3669–79. doi: 10.4161/cc.7.23.7164.

Fullerton, M. D., and G. R. Steinberg. 2010. SIRT1 takes a backseat to AMPK in the regulation of insulin sensitivity by resveratrol. *Diabetes* 59 (3):551–3. doi: 10.2337/db09-1732.

Galleggiante, V., S. De Santis, M. Liso, G. Verna, E. Sommella, M. Mastronardi, P. Campiglia, M. Chieppa, and G. Serino. 2019. Quercetin-induced miR-369-3p suppresses chronic inflammatory response targeting C/EBP-β . *Molecular Nutrition & Food Research* 63 (19):e1801390doi: 10.1002/mnfr.201801390.

Gerhart-Hines, Z., J. T. Rodgers, O. Bare, C. Lerin, S. H. Kim, R. Mostoslavsky, F. W. Alt, Z. Wu, and P. Puigserver. 2007. Metabolic control of muscle mitochondrial function and fatty acid oxidation through SIRT1/PGC-1alpha. *The EMBO Journal* 26 (7):1913–23. doi: 10.1038/sj.emboj.7601633.

Gonzales, A. M., and R. A. Orlando. 2008. Curcumin and resveratrol inhibit nuclear factor-kappaB-mediated cytokine expression in adipocytes. *Nutrition & Metabolism* 5:17doi: 10.1186/1743-7075-5-17.

Han, X., T. Shen, and H. Lou. 2007. Dietary polyphenols and their biological significance. *International Journal of Molecular Sciences* 8 (9): 950–88. doi: 10.3390/i8090950.

Hao, J., W. Shen, G. Yu, H. Jia, X. Li, Z. Feng, Y. Wang, P. Weber, K. Wertz, E. Sharman, et al. 2010. Hydroxytyrosol promotes mitochondrial biogenesis and mitochondrial function in 3T3-L1 adipocytes. *The Journal of Nutritional Biochemistry* 21 (7):634–44. doi: 10.1016/j.jnutbio.2009.03.012.

Harp, J. B. 2004. New insights into inhibitors of adipogenesis. *Current Opinion in Lipidology* 15 (3):303–7. doi: 10.1097/00041433-200406000-00010.

He, W., Y. Barak, A. Hevener, P. Olson, D. Liao, J. Le, M. Nelson, E. Ong, J. M. Olefsky, and R. M. Evans. 2003. Adipose-specific peroxisome proliferator-activated receptor gamma knockout causes insulin resistance in fat and liver but not in muscle. *Proceedings of the National Academy of Sciences of the United States of America* 100 (26):15712–7. doi: 10.1073/pnas.2536828100.

Hou, X., S. Xu, K. A. Maitland-Toolan, K. Sato, B. Jiang, Y. Ido, F. Lan, K. Walsh, M. Wierzbicki, T. J. Verbeuren, et al. 2008. SIRT1 regulates hepatocyte lipid metabolism through activating AMP-activated protein kinase. *The Journal of Biological Chemistry* 283 (29): 20015–26. doi: 10.1074/jbc.M802187200.

Huang, J., Y. Wang, Z. Xie, Y. Zhou, Y. Zhang, and X. Wan. 2014. The anti-obesity effects of green tea in human intervention and basic molecular studies. *European Journal of Clinical Nutrition* 68 (10): 1075–87. doi: 10.1038/ejcn.2014.143.

Humbyrd, C. J. 2018. Complex Obesity: Multifactorial Etiologies and Multifaceted Responses. *The American Journal of Bioethics: AJOB* 18 (7):87–9. doi: 10.1080/15265161.2018.1478042.

Hung, P. F., B. T. Wu, H. C. Chen, Y. H. Chen, C. L. Chen, M. H. Wu, H. C. Liu, M. J. Lee, and Y. H. Kao. 2005. Antimitogenic effect of green tea (–)-epigallocatechin gallate on 3T3-L1 preadipocytes depends on the ERK and Cdk2 pathways. *American Journal of Physiology. Cell Physiology* 288 (5):C1094–108. doi: 10.1152/ajpcell.00569.2004.

Ivanov, V. N., M. A. Partridge, G. E. Johnson, S. X. Huang, H. Zhou, and T. K. Hei. 2008. Resveratrol sensitizes melanomas to TRAIL through modulation of antiapoptotic gene expression. *Experimental Cell Research* 314 (5):1163–76. doi: 10.1016/j.yexcr.2007.12.012.

Jaacks, L. M., S. Vandevijvere, A. Pan, C. J. McGowan, C. Wallace, F. Imamura, D. Mozaffarian, B. Swinburn, and M. Ezzati. 2019. The obesity transition: Stages of the global epidemic. *The Lancet. Diabetes & Endocrinology* 7 (3):231–40. doi: 10.1016/S2213-8587(19)30026-9.

Kalupahana, N. S., N. Moustaid-Moussa, and K. J. Claycombe. 2012. Immunity as a link between obesity and insulin resistance. *Molecular Aspects of Medicine* 33 (1):26–34. doi: 10.1016/j.mam.2011.10.011.

Kang, G. G., N. Francis, R. Hill, D. Waters, C. Blanchard, and A. B. Santhakumar. 2019. Dietary polyphenols and gene expression in molecular pathways associated with Type 2 diabetes mellitus: A review. *International Journal of Molecular Sciences* 21. doi: 10.3390/ijms21010140.

Kang I., J. C. Espin, T. P. Carr, F. A. Tomas-Barberan and S. Chung. 2016. Raspberry seed flour attenuates high-sucrose diet-mediated hepatic stress and adipose tissue inflammation. *Journal of Nutrition Biochem Raspberry seed flour attenuates high-sucrose diet-mediated hepatic stress and adipose tissue inflammation* 32:64–72.

Kang, L., W. Heng, A. Yuan, L. Baolin, and H. Fang. 2010. Resveratrol modulates adipokine expression and improves insulin sensitivity in adipocytes: Relative to inhibition of inflammatory responses. *Biochimie* 92 (7):789–96. doi: 10.1016/j.biochi.2010.02.024.

Kershaw, E. E., and J. S. Flier. 2004. Adipose tissue as an endocrine organ. *The Journal of Clinical Endocrinology and Metabolism* 89 (6): 2548–56. doi: 10.1210/jc.2004-0395.

Kim, C. Y., T. T. Le, C. Chen, J. X. Cheng, and K. H. Kim. 2011a. Curcumin inhibits adipocyte differentiation through modulation of mitotic clonal expansion. *The Journal of Nutritional Biochemistry* 22 (10):910–20. doi: 10.1016/j.jnutbio.2010.08.003.

Kim, H., A. Hiraishi, K. Tsuchiya, and K. Sakamoto. 2010. (–) Epigallocatechin gallate suppresses the differentiation of 3T3-L1 preadipocytes through transcription factors FoxO1 and SREBP1c. *Cytotechnology*62 (3):245–55. doi: 10.1007/s10616-010-9285-x.

Kim, S., Y. Jin, Y. Choi, and T. Park. 2011b. Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice. *Biochemical Pharmacology* 81 (11):1343–51. doi: 10.1016/j.bcp.2011.03.012.

Klaus, S., S. Pultz, C. Thone-Reineke, and S. Wolfram. 2005. Epigallocatechin gallate attenuates diet-induced obesity in mice by decreasing energy absorption and increasing fat oxidation. *International Journal of Obesity (2005)* 29 (6):615–23. doi: 10.1038/sj.ijo.0802926.

Kudo, N., Y. Arai, Y. Suhara, T. Ishii, T. Nakayama, and N. Osakabe. 2015. A single oral administration of theaflavins increases energy expenditure and the expression of metabolic genes. *PLoS One* 10 (9):e0137809doi: 10.1371/journal.pone.0137809.

Kumar Singh, A., C. Cabral, R. Kumar, R. Ganguly, H. Kumar Rana, A. Gupta, M. Rosaria Lauro, C. Carbone, F. Reis, and A. K. Pandey. 2019. Beneficial effects of dietary polyphenols on gut microbiota and strategies to improve delivery efficiency. *Nutrients*11 (9):2216. doi: 10.3390/nu11092216.

Kwon, J. Y., S. G. Seo, S. Yue, J. X. Cheng, K. W. Lee, and K. H. Kim. 2012. An inhibitory effect of resveratrol in the mitotic clonal expansion and insulin signaling pathway in the early phase of adipogenesis. *Nutrition Research (New York, N.Y.)* 32 (8):607–16. doi: 10.1016/j.nutres.2012.06.014.

Lagouge, M., C. Argmann, Z. Gerhart-Hines, H. Meziane, C. Lerin, F. Daussin, N. Messadeq, J. Milne, P. Lambert, P. Elliott, et al. 2006. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell Resveratrol*127 (6):1109–22. doi: 10.1016/j.cell.2006.11.013.

Lan, F., J. M. Cacicedo, N. Ruderman, and Y. Ido. 2008. SIRT1 modulation of the acetylation status, cytosolic localization, and activity of LKB1. Possible role in AMP-activated protein kinase activation. *The Journal of Biological Chemistry* 283 (41):27628–35. doi: 10.1074/jbc.M805711200.

Lasa, A., M. Schweiger, P. Kotzbeck, I. Churruca, E. Simon, R. Zechner, and M. P. Portillo. 2012. Resveratrol regulates lipolysis via adipose triglyceride lipase. *The Journal of Nutritional Biochemistry* 23 (4):379–84. doi: 10.1016/j.jnutbio.2010.12.014.

Lee, M. S., C. T. Kim, I. H. Kim, and Y. Kim. 2009a. Inhibitory effects of green tea catechin on the lipid accumulation in 3T3-L1 adipocytes. *Phytotherapy Research : PTR* 23 (8):1088–91. doi: 10.1002/ptr.2737.

Lee, M. S., C. T. Kim, and Y. Kim. 2009b. Green tea (–)-epigallocatechin-3-gallate reduces body weight with regulation of multiple genes expression in adipose tissue of diet-induced obese mice. *Annals of Nutrition and Metabolism* 54 (2):151–7. doi: 10.1159/000214834.

Lee, M. S., and Y. Kim. 2009c. (–)-Epigallocatechin-3-gallate enhances uncoupling protein 2 gene expression in 3T3-L1 adipocytes. *Bioscience, Biotechnology, and Biochemistry* 73 (2):434–6. doi: 10.1271/bbb.80563.

Lee, M. S., Y. Shin, S. Jung, and Y. Kim. 2017. Effects of epigallocatechin-3-gallate on thermogenesis and mitochondrial biogenesis in brown adipose tissues of diet-induced obese mice. *Food & Nutrition Research* 61 (1):1325307doi: 10.1080/16546628.2017.1325307.

Lee, Y. K., W. S. Lee, J. T. Hwang, D. Y. Kwon, Y. J. Surh, and O. J. Park. 2009d. Curcumin exerts antidifferentiation effect through AMPKalpha-PPAR-gamma in 3T3-L1 adipocytes and antiproliferatory effect through AMPKalpha-COX-2 in cancer cells. *Journal of Agricultural and Food Chemistry* 57 (1):305–10. doi: 10.1021/jf802737z.

Lee, Y. S., J. Wollam, and J. M. Olefsky. 2018. An integrated view of immunometabolism. *Cell* 172 (1-2):22–40. doi: 10.1016/j.cell.2017.12.025.

Lin, S. C., and D. G. Hardie. 2018. AMPK: Sensing glucose as well as cellular energy status. *Cell Metabolism* 27 (2):299–313. doi: 10.1016/j.cmet.2017.10.009.

Liu, H. S., Y. H. Chen, P. F. Hung, and Y. H. Kao. 2006. Inhibitory effect of green tea (–)-epigallocatechin gallate on resistin gene expression in 3T3-L1 adipocytes depends on the ERK pathway. *American Journal of Physiology. Endocrinology and Metabolism* 290 (2):E273–81. doi: 10.1152/ajpendo.00325.2005.

Liu, X., H. Zhao, Q. Jin, W. You, H. Cheng, Y. Liu, E. Song, G. Liu, X. Tan, X. Zhang, et al. 2018. Resveratrol induces apoptosis and inhibits adipogenesis by stimulating the SIRT1-AMPKα-FOXO1 signalling pathway in bovine intramuscular adipocytes . *Molecular and Cellular Biochemistry* 439 (1–2):213–23. doi: 10.1007/s11010-017-3149-z.

Lu C., W. Zhu, C. L. Shen and W. Gao. 2012. Green tea polyphenols reduce body weight in rats by modulating obesity-related genes. *PLoS One Green tea polyphenols reduce body weight in rats by modulating obesity-related genes* 7:e38332. doi: 10.1371/journal.pone.0038332.

Lumeng, C. N., J. L. Bodzin, and A. R. Saltiel. 2007. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. *The Journal of Clinical Investigation* 117 (1):175–84. doi: 10.1172/JCI29881.

Magrone, T., and E. Jirillo. 2015. Childhood obesity: Immune response and nutritional approaches. *Frontiers in Immunology* 6:76doi: 10.3389/fimmu.2015.00076.

Manach, C., G. Williamson, C. Morand, A. Scalbert, and C. Remesy. 2005. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *The American Journal of Clinical Nutrition* 81 (1 Suppl):230S–42S. doi: 10.1093/ajcn/81.1.230S.

Marin, L., E. M. Miguelez, C. J. Villar, and F. Lombo. 2015. Bioavailability of dietary polyphenols and gut microbiota metabolism: Antimicrobial properties. *BioMed Research International* 2015: 905215doi: 10.1155/2015/905215.

Marzano, F., M. F. Faienza, M. F. Caratozzolo, G. Brunetti, M. Chiara, D. S. Horner, A. Annese, A. M. D'Erchia, A. Consiglio, G. Pesole, et al. 2018. Pilot study on circulating miRNA signature in children with obesity born small for gestational age and appropriate for gestational age. *Pediatric Obesity* 13 (12):803–11. doi: 10.1111/ijpo.12439.

Mathis, D. 2013. Immunological goings-on in visceral adipose tissue. *Cell Metabolism* 17 (6):851–9. doi: 10.1016/j.cmet.2013.05.008.

Mele, L., G. Bidault, P. Mena, A. Crozier, F. Brighenti, A. Vidal-Puig, and D. Del Rio. 2017. Dietary (poly)phenols, brown adipose tissue activation, and energy expenditure: A narrative review. *Advances in Nutrition: An International Review Journal* 8 (5):694–704. doi: 10.3945/an.117.015792.

Mennen, L. I., R. Walker, C. Bennetau-Pelissero, and A. Scalbert. 2005. Risks and safety of polyphenol consumption. *The American Journal of Clinical Nutrition* 81 (1 Suppl):326S–9S. doi: 10.1093/ajcn/81.1.326S.

Meydani, M., and S. T. Hasan. 2010. Dietary polyphenols and obesity. *Nutrients* 2 (7):737–51. doi: 10.3390/nu2070737.

Miniello, V. L., M. F. Faienza, P. Scicchitano, F. Cortese, M. Gesualdo, A. Zito, M. Basile, P. Recchia, D. Leogrande, D. Viola, et al. 2014. Insulin resistance and endothelial function in children and adolescents. *International Journal of Cardiology* 174 (2):343–7. doi: 10.1016/j.ijcard.2014.04.115.

Monika P. and A. Geetha. 2015. The modulating effect of Persea americana fruit extract on the level of expression of fatty acid synthase complex, lipoprotein lipase, fibroblast growth factor-21 and leptin – A biochemical study in rats subjected to experimental hyperlipidemia and obesity. *Phytomedicine The modulating effect of Persea americana fruit extract on the level of expression of fatty acid synthase complex, lipoprotein lipase, fibroblast growth factor-21 and leptin – A biochemical study in rats subjected to experimental hyperlipidemia and obesity* 22:939–45.

Most, J., I. Warnke, M. V. Boekschoten, J. W. E. Jocken, P. de Groot, A. Friedel, I. Bendik, G. H. Goossens, and E. E. Blaak. 2018. The effects of polyphenol supplementation on adipose tissue morphology and gene expression in overweight and obese humans. *Adipocyte*7 (3):190–6. doi: 10.1080/21623945.2018.1469942.

Nacci, C., V. Leo, L. De Benedictis, M. R. Carratu, N. Bartolomeo, M. Altomare, P. Giordano, M. F. Faienza, and M. Montagnani. 2013. Elevated endothelin-1 (ET-1) levels may contribute to hypoadiponectinemia in childhood obesity. *The Journal of Clinical Endocrinology & Metabolism* 98 (4):E683–93. doi: 10.1210/jc.2012-4119.

Nagao, K., T. Jinnouchi, S. Kai, and T. Yanagita. 2013. Effect of dietary resveratrol on the metabolic profile of nutrients in obese OLETF rats. *Lipids in Health and Disease* 12:8doi: 10.1186/1476-511X-12-8.

O'Neill, H. M., G. P. Holloway, and G. R. Steinberg. 2013. AMPK regulation of fatty acid metabolism and mitochondrial biogenesis: Implications for obesity. *Molecular and Cellular Endocrinology* 366 (2):135–51. doi: 10.1016/j.mce.2012.06.019.

Odegaard, J. I., and A. Chawla. 2011. Alternative macrophage activation and metabolism. *Annual Review of Pathology* 6:275–97. doi: 10.1146/annurev-pathol-011110-130138.

Olholm, J., S. K. Paulsen, K. B. Cullberg, B. Richelsen, and S. B. Pedersen. 2010. Anti-inflammatory effect of resveratrol on adipokine expression and secretion in human adipose tissue explants. *International Journal of Obesity* 34 (10):1546–53. doi: 10.1038/ijo.2010.98.

Ooi, J., H. A. Adamu, M. U. Imam, H. Ithnin, and M. Ismail. 2018. Polyphenol-rich ethyl acetate fraction isolated from Molineria latifolia ameliorates insulin resistance in experimental diabetic rats via IRS1/AKT activation. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie* 98:125–33. doi: 10.1016/j.biopha.2017.12.002.

Ordovas, J. M., L. R. Ferguson, E. S. Tai, and J. C. Mathers. 2018. Personalised nutrition and health. *British Medical Journal* 361:2173. doi: 10.1136/bmj.k2173.

Ottaviani, J. I., G. Borges, T. Y. Momma, J. P. Spencer, C. L. Keen, A. Crozier, and H. Schroeter. 2016. The metabolome of [2-(14)C](–)-epicatechin in humans: Implications for the assessment of efficacy, safety, and mechanisms of action of polyphenolic bioactives. *Scientific Reports* 6 (1):29034. doi: 10.1038/srep29034.

Paipilla, A. T-d A. C., J. J. Cruz-Sanchez, H. Castro, E. Poveda-Espinosa, A. Camacho, and A. L. de la Garza. 2016. Effect of dietary interventions in the gene expression involved in molecular

mechanisms of obesity: Evidence-based translational research from clinical trials. *EC Nutrition* 5:1255–65.

Park, H. J., D. A. DiNatale, M. Y. Chung, Y. K. Park, J. Y. Lee, S. I. Koo, M. O'Connor, J. E. Manautou, and R. S. Bruno. 2011. Green tea extract attenuates hepatic steatosis by decreasing adipose lipogenesis and enhancing hepatic antioxidant defenses in ob/ob mice. *The Journal of Nutritional Biochemistry* 22 (4):393–400. doi: 10.1016/j.jnutbio.2010.03.009.

Pena-Romero, A. C., D. Navas-Carrillo, F. Marin, and E. Orenes-Pinero. 2018. The future of nutrition: Nutrigenomics and nutrigenetics in obesity and cardiovascular diseases. *Critical Reviews in Food Science and Nutrition* 58 (17):3030–41. doi: 10.1080/10408398.2017.1349731.

Peyrol, J., C. Riva, and M. J. Amiot. 2017. Hydroxytyrosol in the Prevention of the Metabolic Syndrome and Related Disorders. *Nutrients*9 (3):306. doi: 10.3390/nu9030306.

Pinto, P., and C. N. Santos. 2017. Worldwide (poly)phenol intake: Assessment methods and identified gaps. *European Journal of Nutrition* 56 (4):1393–408. doi: 10.1007/s00394-016-1354-2.

Poddar, K., S. Kolge, L. Bezman, G. E. Mullin, and L. J. Cheskin. 2011. Nutraceutical supplements for weight loss: A systematic review. *Nutrition in Clinical Practice: Official Publication of the American Society for Parenteral and Enteral Nutrition* 26 (5):539–52. doi: 10.1177/0884533611419859.

Qiao, L., and J. Shao. 2006. SIRT1 regulates adiponectin gene expression through Foxo1-C/enhancer-binding protein alpha transcriptional complex. *The Journal of Biological Chemistry* 281 (52):39915–24. doi: 10.1074/jbc.M607215200.

Radler, U., H. Stangl, S. Lechner, G. Lienbacher, R. Krepp, E. Zeller, M. Brachinger, D. Eller-Berndl, A. Fischer, C. Anzur, et al. 2011. A combination of (omega-3) polyunsaturated fatty acids, polyphenols and L-carnitine reduces the plasma lipid levels and increases the expression of genes involved in fatty acid oxidation in human peripheral blood mononuclear cells and HepG2 cells. *Annals of Nutrition and Metabolism* 58 (2):133–40. doi: 10.1159/000327150.

Rayalam, S., J. Y. Yang, S. Ambati, M. A. Della-Fera, and C. A. Baile. 2008. Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. *Phytotherapy Research* 22 (10):1367–71. doi: 10.1002/ptr.2503.

Renaud, J., and M. G. Martinoli. 2019. Considerations for the use of polyphenols as therapies in neurodegenerative diseases. *International Journal of Molecular Sciences* 20. doi :10.3390/ijms20081883.

Ridaura, V. K., J. J. Faith, F. E. Rey, J. Cheng, A. E. Duncan, A. L. Kau, N. W. Griffin, V. Lombard, B. Henrissat, J. R. Bain, et al. 2013. Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science (New York, N.Y.)* 341 (6150):1241214 doi: 10.1126/science.1241214.

Riva, A., F. Borgo, C. Lassandro, E. Verduci, G. Morace, E. Borghi, and D. Berry. 2017. Pediatric obesity is associated with an altered gut microbiota and discordant shifts in Firmicutes populations. *Environmental Microbiology* 19 (1):95–105. doi: 10.1111/1462-2920.13463.

Rodgers, J. T., C. Lerin, W. Haas, S. P. Gygi, B. M. Spiegelman, and P. Puigserver. 2005. Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature* 434 (7029):113–8. doi: 10.1038/nature03354.

Roopchand, D. E., R. N. Carmody, P. Kuhn, K. Moskal, P. Rojas-Silva, P. J. Turnbaugh, and I. Raskin. 2015. Dietary polyphenols promote growth of the gut bacterium Akkermansia muciniphila and attenuate high-fat diet-induced metabolic syndrome. *Diabetes*64 (8):2847–58. doi: 10.2337/db14-1916.

Roth, C. L., M. Kratz, M. M. Ralston, and T. Reinehr. 2011. Changes in adipose-derived inflammatory cytokines and chemokines after successful lifestyle intervention in obese children. *Metabolism* 60 (4):445–52. doi: 10.1016/j.metabol.2010.03.023.

Sanchez, J.,. T. Priego, C. Pico, W. Ahrens, S. De Henauw, A. Fraterman, S. Marild, D. Molnar, L. A. Moreno, J. Peplies, et al. 2012. Blood cells as a source of transcriptional biomarkers of childhood obesity and its related metabolic alterations: Results of the IDEFICS study. *The Journal of Clinical Endocrinology and Metabolism* 97 (4):E648–52. doi: 10.1210/jc.2011-2209.

Scherer, P. E. 2006. Adipose tissue: From lipid storage compartment to endocrine organ. *Diabetes*55 (6):1537–45. doi: 10.2337/db06-0263.

Schilter, B.,. C. Andersson, R. Anton, A. Constable, J. Kleiner, J. O'Brien, A. G. Renwick, O. Korver, F. Smit, and R. Walker. 2003. Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. *Food and Chemical Toxicology: Toxicology* 41 (12):1625–49. doi: 10.1016/S0278-6915(03)00221-7.

Scoditti, E., S. Carpi, M. Massaro, M. Pellegrino, B. Polini, M. A. Carluccio, M. Wabitsch, T. Verri, P. Nieri, and R. D. Caterina. 2019. Hydroxytyrosol modulates adipocyte gene and miRNA expression under inflammatory condition. *Nutrients* 11 (10):2493. doi: 10.3390/nu11102493.

Serreli, G., and M. Deiana. 2019. In vivo formed metabolites of polyphenols and their biological efficacy. *Food & Function* 10 (11):6999–7021. doi: 10.1039/c9fo01733j.

Singer, K., and C. N. Lumeng. 2017. The initiation of metabolic inflammation in childhood obesity. *The Journal of Clinical Investigation* 127 (1):65–73. doi: 10.1172/JCI88882.

Spencer, J. P., M. M. Abd El Mohsen, A. M. Minihane, and J. C. Mathers. 2008. Biomarkers of the intake of dietary polyphenols: Strengths, limitations and application in nutrition research. *The British Journal of Nutrition* 99 (1):12–22. doi: 10.1017/S0007114507798938.

Torabi, S., and N. M. DiMarco. 2016. Original research: Polyphenols extracted from grape powder induce lipogenesis and glucose uptake during differentiation of murine preadipocytes. *Experimental Biology and Medicine (Maywood, N.J.)* 241 (16):1776–85. doi: 10.1177/1535370216645213.

Tsao, R. 2010. Chemistry and biochemistry of dietary polyphenols. *Nutrients* 2 (12):1231–46. doi: 10.3390/nu2121231.

Tsuda, T.,. Y. Ueno, T. Yoshikawa, H. Kojo, and T. Osawa. 2006. Microarray profiling of gene expression in human adipocytes in response to anthocyanins. *Biochemical Pharmacology* 71 (8):1184–97. doi: 10.1016/j.bcp.2005.12.042.

Venkatakrishnan, K., H. F. Chiu, and C. K. Wang. 2019. Extensive review of popular functional foods and nutraceuticals against obesity and its related complications with a special focus on randomized clinical trials. *Food & Function* 10 (5):2313–29. doi: 10.1039/c9fo00293f.

Visioli, F., C. A. De La Lastra, C. Andres-Lacueva, M. Aviram, C. Calhau, A. Cassano, M. D'Archivio, A. Faria, G. Fave, V. Fogliano, et al. 2011. Polyphenols and human health: A prospectus. *Critical Reviews in Food Science and Nutrition* 51 (6):524–46. doi: 10.1080/10408391003698677.

Walker, C. G., M. G. Zariwala, M. J. Holness, and M. C. Sugden. 2007. Diet, obesity and diabetes: A current update. *Clinical Science (London, England : 1979)* 112 (2):93–111. doi: 10.1042/CS20060150.

Wang, S., N. Moustaid-Moussa, L. Chen, H. Mo, A. Shastri, R. Su, P. Bapat, I. Kwun, and C. L. Shen. 2014. Novel insights of dietary polyphenols and obesity. *The Journal of Nutritional Biochemistry* 25 (1):1–18. doi: 10.1016/j.jnutbio.2013.09.001.

Wang, S. L., Y. Li, Y. Wen, Y. F. Chen, L. X. Na, S. T. Li, and C. H. Sun. 2009. Curcumin, a potential inhibitor of up-regulation of TNF-alpha and IL-6 induced by palmitate in 3T3-L1 adipocytes through NF-kappaB and JNK pathway. *Biomedical and Environmental Sciences : BES* 22 (1):32–9. doi: 10.1016/S0895-3988(09)60019-2.

Wang, Y., and L. V. Hooper. 2019. Immune control of the microbiota prevents obesity. *Science (New York, N.Y.)* 365 (6451):316–7. doi: 10.1126/science.aay2057.

Weihrauch-Bluher, S., P. Schwarz, and J. H. Klusmann. 2019. Childhood obesity: Increased risk for cardiometabolic disease and cancer in adulthood. *Metabolism: clinical and Experimental* 92:147–52. doi: 10.1016/j.metabol.2018.12.001.

Weisberg, S. P., R. Leibel, and D. V. Tortoriello. 2008. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity.

Endocrinology Dietary Endocrinology 149 (7):3549–58. doi: 10.1210/en.2008-0262.

WHO. 2018. *Childhood overweight and obesity*. Copenhagen, Denmark: WHO Regional Office for Europe UN City.

Wolfram, S., D. Raederstorff, Y. Wang, S. R. Teixeira, V. Elste, and P. Weber. 2005. TEAVIGO (epigallocatechin gallate) supplementation prevents obesity in rodents by reducing adipose tissue mass. *Annals of Nutrition and Metabolism* 49 (1):54–63. doi: 10.1159/000084178.

Wu, T., Q. Tang, Z. Gao, Z. Yu, H. Song, X. Zheng, and W. Chen. 2013. Blueberry and mulberry juice prevent obesity development in C57BL/6 mice. *PLoS One* 8 (10):e77585doi: 10.1371/journal.pone.0077585.

Yamaguchi, S., H. Katahira, S. Ozawa, Y. Nakamichi, T. Tanaka, T. Shimoyama, K. Takahashi, K. Yoshimoto, M. O. Imaizumi, S. Nagamatsu, et al. 2005. Activators of AMP-activated protein kinase enhance GLUT4 translocation and its glucose transport activity in 3T3-L1 adipocytes. *American Journal of Physiology. Endocrinology and Metabolism* 289 (4):E643–9. doi: 10.1152/ajpendo.00456.2004.

Zhang, H. Y., Z. X. Du, and X. Meng. 2013. Resveratrol prevents TNFα-induced suppression of adiponectin expression via PPARγ activation in 3T3-L1 adipocytes. *Clinical and Experimental Medicine* 13 (3):193–9. doi: 10.1007/s10238-012-0189-2.

Zhang, X. H., B. Huang, S. K. Choi, and J. S. Seo. 2012. Anti-obesity effect of resveratrol-amplified grape skin extracts on 3T3-L1 adipocytes differentiation. *Nutrition Research and Practice* 6 (4): 286–93. doi: 10.4162/nrp.2012.6.4.286.

Zhang, Z.,. H. Zhang, B. Li, X. Meng, J. Wang, Y. Zhang, S. Yao, Q. Ma, L. Jin, J. Yang, et al. 2014. Berberine activates thermogenesis in white and brown adipose tissue. *Nature Communications* 5:5493doi: 10.1038/ncomms6493.

Zhao, J., X. B. Sun, F. Ye, and W. X. Tian. 2011. Suppression of fatty acid synthase, differentiation and lipid accumulation in adipocytes by curcumin. *Molecular and Cellular Biochemistry* 351 (1-2):19–28. doi: 10.1007/s11010-010-0707-z.

Zhu, J., W. Yong, X. Wu, Y. Yu, J. Lv, C. Liu, X. Mao, Y. Zhu, K. Xu, X. Han, et al. 2008. Anti-inflammatory effect of resveratrol on TNF-alpha-induced MCP-1 expression in adipocytes. *Biochemical and Biophysical Research Communications* 369 (2):471–7. doi: 10.1016/j.bbrc.2008.02.034.