Do flavanols-rich natural products relieve obesity-related insulin resistance?

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ARTICLE INFO

Keywords:
Insulin resistance
Obesity
Polyphenols
Cocoa
Coffee
G protein-coupled estrogen receptor

ABSTRACT

Growing evidence support that insulin resistance may occur as a severe problem due to chronic energetic overfeeding and subsequent obesity. When an abundance of glucose and saturated fat enter the cell, impaired blood flow, hypoxia, inflammation and macrophage infiltration in obese adipose tissue may induce oxidative stress and insulin resistance. Excessive circulating saturated fatty acids ectopically accumulate in insulin-sensitive tissues and impair insulin action. In this context, excessive hepatic lipid accumulation may play a central, pathogenic role in insulin resistance. It is thought that dietary polyphenols may ameliorate obesity-related insulin resistance by attenuating inflammatory responses and oxidative stress. The most often occurring natural polyphenolic compounds are flavonoids. In this review, the possible mechanistic effect of flavonoid-rich natural products on insulin resistance-related metabolic pathways is discussed. Polyphenol intake can prevent high-fat-diet-induced insulin resistance via cell surface G protein-coupled estrogen receptors by upregulating the expression of related genes, and their pathways, which are responsible for the insulin sensitivity.

1. Introduction

Overweight and obesity are expected to raise up to 89% and 85% in males and females, respectively by the year 2030. As a result, the obesity-related prevalence of coronary heart diseases will increase by 97%, while cancers will elevate by 61% and type 2 diabetes will raise by 21%. Thereby, total healthcare costs for major obesity-related conditions will increase from 2.55 billion Euro to 5.4 billion by 2030 (Engin, 2017; Keaver et al., 2013). As a consequence, worldwide increased prevalence of obesity and diabetes results in a significant economic impact which constitutes a remarkable portion of healthcare expenditure (Shamseddeen et al., 2011). Genome-wide studies found 97 body mass index (BMI)-associated loci, 56 of which are novel and suggest a role of the central nervous system in developing obesity. These findings suggest that synaptic function, glutamate signaling, insulin secretion, energy metabolism, and adipogenesis may be genetically determined (Locke et al., 2015). Additionally, due to the profound effects of insulin in the pathogenesis of cognitive impairment and neurodegeneration, there is growing evidence suggesting that insulin is a key player in cognitive functions. Impaired brain insulin signaling in the advancement of cognitive dysfunction is relevant to the pathophysiologic mechanisms of cognitive impairment and the risk of developing dementia (Kalmijn et al., 2000; Ma et al., 2015). High glucose is an independent risk factor for insulin resistance in human cortical neurons. Both mitochondrial dysfunction and impaired insulin signaling are the critical biochemical features in the high glucose-related neuronal dysfunction (Peng et al., 2016). In this context, insulin resistance is the result of a long-term process that is encountered by chronic energetic overfeeding, when an abundance of glucose and saturated fat enter the cell. Impaired blood flow, hypoxia, inflammation and macrophage infiltration are interrelated in obese adipose tissue. They altogether may induce oxidative stress and insulin resistance (Goossens, 2008; Roberts et al., 2013).

2. Obesity-related insulin resistance

Hypertrophic adipocytes secrete low levels of tumor necrosis factor-alpha (TNF-alpha), which stimulate preadipocytes and endothelial cells to produce Monocyte Chemoattractant Protein-1 (MCP-1), in turn, responsible for attracting macrophages to the adipose tissue, thus developing a state of chronic low-grade inflammation which is causally linked to insulin resistance. Eventually, the excess of circulating free fatty acids, TNF-alpha and other factors induce insulin resistance (Capurso and Capurso, 2012) (Fig. 1). The inappropriately excessive dietary fat intake that is accompanied by peripheral insulin resistance promotes triglycerides hydrolysis, and these contribute to the increase
in the blood free fatty acid concentration (Sanyal et al., 2001). Eventually, in the insulin-sensitive tissues, the released excessive circulating fatty acids may ectopically accumulate and may impair the insulin action. This influence on the whole-body insulin sensitivity is related to the elevation in the basal lipolysis levels that alters the secretory profile of adipose tissue. Finally, the excessive fatty acid release may also worsen adipose tissue inflammation, which is a well-known parameter contributing to insulin resistance (Morigny et al., 2016). Accumulation of bioactive lipid species, diacylglycerol, and ceramides, have been demonstrated to play essential roles in the establishment of insulin resistance in insulin-sensitive tissues by activating proinflammatory signaling pathways and protein kinase C isoforms (PKC) (Turban and Hajduch, 2011). On the one hand, diacylglycerol-activated PKC inhibits insulin receptor substrate (IRS)-1 by increasing the phosphorylation on its Ser636/639 residues (Mack et al., 2008). On the other hand, ceramides induce the recruitment and retention of both PKC and protein kinase B (PKB/Akt) in caveolin-enriched microdomains of the plasma membrane. The accumulation of PKB significantly contributes to ceramide-induced inhibition of PKB-directed signaling (Fox et al., 2007; Hajduch et al., 2008). Consequently, ceramides repress insulin signaling through segregation of both PKB/PKC in these sub-microdomains of adipocytes and muscle cells (Turban and Hajduch, 2011). Ceramide-induced inactivation of PKB/Akt via activation of atypical PKC isoforms (aPKCs) is the second mechanism of insulin resistance (Hage Hassan et al., 2014). Many researchers agree that impaired insulin action occurs at the level of IRS-1 following stress kinases activation, such as c-Jun N-terminal kinase (JNK) and nuclear factor-kappaB (IkappaB) kinase (IKK)beta. Eventually phosphorylation of IRS-1 decreases (Aguirre et al., 2000, 2002; Rui et al., 2001). Reduced IRS-1 phosphorylation on critical tyrosine residues prevents binding with p85 of phosphoinositide 3-kinase (PI3K) and subsequently downstream signal transduction. Furthermore, alteration in phosphorylation of serine residues is shown to target IRS-1 for proteasomal degradation. Therefore, glucoregulatory tissues harvested from obese individuals express reduced levels of IRS-1 protein (Ahmad et al., 1997; Pederson et al., 2001; Potashnik et al., 2003; Wang et al., 2009).

Obesity is recognized as a state of chronic, low-grade inflammation and is associated with increased serum markers of inflammation and oxidative stress. Excessive circulating fatty acids ectopically accumulate in insulin-sensitive tissues and impair insulin action. Furthermore macrophage-mediated inflammation induces insulin resistance by causing decreased insulin signaling in target cells, as well. Elevated TNFα and FFA levels in adipose tissue and blood lead to activation of serine kinases, proinflammatory cytokines, reactive oxygen and nitrogen species production and endoplasmic reticulum stress through TNFαR and TLR4 pattern recognition receptors, respectively. Polyphenol intake attenuates high-fat diet-induced inflammatory responses and oxidative stress. Dietary polyphenols prevent insulin resistance through the decreased lipogenesis, and the simultaneous stimulation of fatty acid oxidation due to increased lipolysis, in addition to accelerating adiponectin and GLUT4 expression. It has been thought that polyphenols achieve these effects by upregulating the expression of related genes via GPERs. Abbreviations: FFA, Free fatty acid; TNF-α, Tumor necrosis factor-alpha; TNFαR, Tumor necrosis factor-alpha receptor; NF-κB, Nuclear factor-kappa B; IL-6, Interleukin-6; IL-8, Interleukin-8; MCP-1, Monocyte chemotactic protein-1 (CCL2); IR, Insulin resistance; JNK, c-Jun N-terminal kinase; MAP kinase (MAPK), Mitogen-activated protein kinase kinases; RIP1, Receptor-interacting serine/threonine protein kinase 1; TRADD, tumor necrosis factor receptor type 1-associated death domain protein (adapter protein); IKK, Inhibitor kappa B kinase; TRAF, TNF receptor associated factor-1; PPAR, G protein-coupled estrogen receptor; NO, Nitric oxide; eNOS, Endothelial nitric oxide synthase; IRS, Insulin receptor substrate; ROS, Reactive oxygen radicals; TLR4, toll-like receptor-4; PI3K, Phosphoinositide-3-kinase; Nrf2, Nuclear factor erythroid 2-related factor-2; GSH, Green heme oxygenase-1, HO-1, heme oxygenase-1.

Fig. 1. Obesity is a state of chronic, low-grade adipose tissue inflammation and is associated with increased serum markers of inflammation and mitochondrial oxidative stress. Excessive circulating fatty acids ectopically accumulate in insulin-sensitive tissues and impair insulin action. Furthermore macrophage-mediated inflammation induces insulin resistance by causing decreased insulin signaling in target cells, as well. Elevated TNFα and FFA levels in adipose tissue and blood lead to activation of serine kinases, proinflammatory cytokines, reactive oxygen and nitrogen species production and endoplasmic reticulum stress through TNFαR and TLR4 pattern recognition receptors, respectively. Polyphenol intake attenuates high-fat diet-induced inflammatory responses and oxidative stress. Dietary polyphenols prevent insulin resistance through the decreased lipogenesis, and the simultaneous stimulation of fatty acid oxidation due to increased lipolysis, in addition to accelerating adiponectin and GLUT4 expression. It has been thought that polyphenols achieve these effects by upregulating the expression of related genes via GPERs. Abbreviations: FFA, Free fatty acid; TNF-α, Tumor necrosis factor-alpha; TNFαR, Tumor necrosis factor-alpha receptor; NF-κB, Nuclear factor-kappa B; IL-6, Interleukin-6; IL-8, Interleukin-8; MCP-1, Monocyte chemotactic protein-1 (CCL2); IR, Insulin resistance; JNK, c-Jun N-terminal kinase; MAP kinase (MAPK), Mitogen-activated protein kinase kinases; RIP1, Receptor-interacting serine/threonine protein kinase 1; TRADD, tumor necrosis factor receptor type 1-associated death domain protein (adapter protein); IKK, Inhibitor kappa B kinase; TRAF, TNF receptor associated factor-1; PPAR, G protein-coupled estrogen receptor; NO, Nitric oxide; eNOS, Endothelial nitric oxide synthase; IRS, Insulin receptor substrate; ROS, Reactive oxygen radicals; TLR4, toll-like receptor-4; PI3K, Phosphoinositide-3-kinase; Nrf2, Nuclear factor erythroid 2-related factor-2; GSH, Green heme oxygenase-1, HO-1, heme oxygenase-1.
white adipose tissue or brown adipose tissue. Although the primary function of white adipose tissue is energy storage, it also functions as an endocrine organ secreting hormones and cytokines—namely adipokines—such as leptin and adiponectin that regulate feeding and metabolism (Cristancho and Lazar, 2011). Thus, a significant number of the adipocyte-derived substances play an intricate role in various aspects of the innate and adaptive immune response (Halberg et al., 2008). Adipose tissue is not merely a storage depot for excess calories, but it also actively releases fatty acids and a variety of polypeptides. Greater than 40% of the total adipose tissue cell content from obese humans can be composed of immune cells, compared with approximately 10% in lean counterparts (Weisberg et al., 2006). In this respect, white adipose tissue contains a unique immune cell repertoire. These include alternatively activated macrophages, invariant natural killer T cells, and regulatory T cells. Impairment in the local leukocyte homeostasis takes part in the obesity-related inflammation and associated metabolic disorders (Exley et al., 2014).

Despite the massive induction of a pro-angiogenic response in obesity, it is not sufficient to prevent the development of hypoxia in the expanding adipose tissue (Halberg et al., 2008). Besides vascular endothelial growth factor, hypoxic adipocytes secrete higher levels of a number of pro-angiogenic factors, such as leptin, interleukin (IL)-6, macrophage migration inhibitory factor (MIF), leptin, and plasminogen activator inhibitor-1 (Wang et al., 2004). In addition to these, the obesity is found to be associated with elevated plasma levels of TNF-alpha, resistin, angiopoietin-1, and heparocyte growth factor (Silha et al., 2005). As mentioned above, chronic activation of intracellular proinflammatory pathways within insulin target cells lead to obesity-related insulin resistance. Several cytokines and chemokines, such as C-C Motif Chemokine Ligand 2 (CCL2), IL-6, IL-1β, MIF, and TNF-alpha, can be released by both adipocytes and macrophages (Halberg et al., 2008; Wang et al., 2008). In insulin resistant and diabetes patients, parallel to the previous data, the proinflammatory cytokynes TNF-alpha and IL-6 have been found to be increased (Tajiri et al., 2005). Furthermore, TNF-alpha levels are elevated in adipose tissue and blood from obese subjects (Hotamisligil et al., 1995). This leads to activation of JNK, IκB kinase, and other serine kinases. In an insulin-resistant state, JNK1 (Bandyopadhyay et al., 2005; Hirosumi et al., 2002) and IKK (Hotamisligil et al., 1995; Itani et al., 2002) signaling is upregulated in insulin-resistant skeletal muscle, fat, and other tissues in humans. Proinflammatory CD11c+ macrophages are responsible for the macrophage-linked fragment of inflammation and insulin resistance (Patsouris et al., 2008). Activated M1 macrophages produce substantial amounts of proinflammatory mediators, such as TNF-alpha, IL-1β, and resistin, that act on adipocytes inducing an insulin-resistant state. In contrast, adipocytes uniquely secrete adipokines, such as leptin and adiponectin (Halberg et al., 2008; Wang et al., 2008), that promote insulin sensitivity, as well as proteins, such as resistin (Steppan et al., 2001) and retinol-binding protein 4 (RBP4) (Yang et al., 2005), that impair insulin sensitivity. A low-calorie diet intervention that significantly decreased body weight and body fat content in nonobietic obese subjects also decreased leptin levels and increased adiponectin levels. As a result of that the leptin-to-adiponectin ratio, a novel marker for insulin sensitivity, significantly improved (Oberhauser et al., 2012). Infiltrated CD8+ T cells are activated by the obese adipose tissue. This process is followed by the promotion of the macrophage recruitment and their subsequent activation in this tissue. On the other hand, CD4+ Foxp3+ T regulatory (Treg) cells are concentrated in the normal abdominal fat, but in insulin-resistant state, their numbers are remarkably and specifically reduced at those sites. These findings demonstrate that the decreased number of Tregs in the insulin resistant obese adipose tissue may create an appropriate environment for the invasion of the inflammatory type macrophages and in turn, this results in a striking release of inflammatory cytokines. Treg cells may have a protective effect to inhibit proinflammatory macrophages, attenuating insulin resistance (Feuerer et al., 2009; Nishimura et al., 2009). While saturated fatty acids are robustly proinflammatory, polyunsaturated fatty acids are weak or neutral, but omega 3 fatty acids are anti-inflammatory (Lee et al., 2001; Solinas et al., 2007; Song et al., 2006). Several studies have also demonstrated that Toll-like pattern recognition receptors, particularly Toll-like receptor (TLR) 4 play important roles in mediating proinflammatory effects of saturated fatty acids in hypertrophic adipose tissue. Macrophage TLR4 expression is increased in obesity. When TLR4 is deleted, saturated fatty acid-induced activation of inflammation is impaired in macrophages, as well as adipocytes and skeletal muscle cells (Nguyen et al., 2007; Shi et al., 2006). In other words, high concentrations of saturated free fatty acids induce proinflammatory effects through TLR2 and TLR4 (Nguyen et al., 2007; Shi et al., 2006). This indicates that in obese conditions, saturated free fatty acids may serve as endogenous TLR4 activator contributors. The transcriptional effects of TLRs result from their regulation of the activities and expression of numerous signal-dependent transcription factors. The major representatives of which are members of the activator protein 1 (AP1), nuclear factor kappaB (NF-kappaB) families and interferon regulatory factors (Takeda and Akira, 2004). Macrophage-mediated inflammation induces insulin resistance in insulin target cells likely proceeds through a two-hit process in which tissue macrophages become activated, releasing cytokines and possibly other factors, which in turn activate inflammatory pathways within the neighboring insulin target cell, causing decreased insulin signaling. Long-chain omega 3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), can exert potent anti-inflammatory effects by inhibiting responses to TNF-alpha (Lee et al., 2003, 2001; Solinas et al., 2007; Song et al., 2006). In addition, the expression of IL-1 has been suggested to contribute to impaired insulin secretion, reduced cell proliferation, and apoptosis of pancreatic beta-cells. It has been shown that a recombinant interleukin-1-receptor antagonist improved glycemia and beta-cell secretory function and reduced markers of systemic inflammation in patients with type 2 diabetes (Larsen et al., 2007). Both the adipocyte and the macrophage serve as important targets for the anti-diabetic effects of peroxisome proliferator-activated receptor gamma (PPAR-gamma) agonists. Adipocytes respond to PPAR-gamma agonist treatment by initiating an anti-inflammatory program with increased secretion of the anti-inflammatory adipokine adiponectin and decreased secretion of pro-inflammatory adipokines, TNF-alpha. Eventually insulin action enhances (Moller and Berger, 2003; Tauchiha et al., 2005).

In case of hyperglycemia, adipocytes accumulate elevated concentrations of reactive oxygen species (ROS), and this status can effectivelly be corrected by mitochondrial respiration inhibitors. Adipocytes cannot downregulate glucose uptake in the presence of increased extracellular glucose levels. Downregulation impairment brings reduced insulin sensitivity of adipocytes, and their consequent reduced ability to increase glucose uptake in response to insulin (Liu et al., 2005). Elevated levels of extracellular glucose cause excessive intracellular glucose concentrations in adipocytes. The over-accumulation of nutrients triggers the production of ROS at the level of mitochondria. A massive load of ROS not only changes the cellular glutathione pool, affecting the redox potential in the secretory pathway but also activates NF-kappaB, triggering a proinflammatory cascade (Scherer, 2006). In addition to proinflammatory cytokines and pattern recognition receptors, cellular stresses activate ROS production and endoplasmic reticulum stress. Systemic markers of oxidative stress increase with adiposity, consistent with a role for ROS in the development of obesity-induced insulin resistance (Keane et al., 2003). One of the potential mechanisms is through the activation of NADPH oxidase by lipid accumulation in the adipocyte, which increases ROS production (Furukawa et al., 2004).

### 3. Hepatic lipid accumulation and insulin resistance

Considering the relationship between intrahepatic lipid metabolism and insulin sensitivity in obesity; one possibility is the excessive hepatic...
lipid accumulation that may play a central, pathogenic role in insulin resistance. The other possibility is that the mitochondrial oxidative capacity may be altered directly by the hepatic insulin resistance (Patti and Corvera, 2010). The elevated levels of mitochondrial fatty acid beta-oxidation rate, in addition to the transfer of electrons to the respiratory chain, result in an imbalance between the high electron input and a restricted outflow. The eventual accumulation and leakage of electrons within the complexes of mitochondrial respiratory chain, cause elevated levels of ROS production. ROS-induced release of TNF-alpha and Fas triggers mitochondrial membrane permeability and apoptosis (Pessayre et al., 2004). In addition, toxic fatty acids can activate the intrinsic apoptosis pathway in hepatocytes via JNK. JNK activation by saturated fatty acids may not only contribute to impaired insulin signaling but also to lipaopoptosis. In this regard, fatty acids-induced JNK stimulation is connected with the mitochondrial pathway of lipaopoptosis that is triggered by the proapoptotic protein Bim-dependent Bax activation in hepatocytes (Malhi et al., 2006; Wree et al., 2011). In this context, the development of peripheral insulin resistance is secondary to hepatic fat infiltration and hepatic insulin resistance (Perseghin, 2009). Reduced mitochondrial function precedes insulin resistance and may thus be the primary event that triggers non-alcoholic fatty liver disease development in obesity (Rector et al., 2010). Activities of mitochondrial respiratory chain complexes are also decreased in liver tissue of patients with non-alcoholic steatohepatitis. Hepatocellular dysfunction correlates with serum TNF-alpha, insulin resistance, and BMI values (Pérez-Carreras et al., 2003). In this case, impairment in the mitochondrial respiratory chain and additional liver lesions indicate the nitration in tyrosine residues of mitochondrial proteins by the peroxynitrite or peroxynitrite derived radicals. Increased hepatic TNF-alpha and inducible nitric oxide synthase (iNOS) expression enhances peroxynitrite formation and subsequent inhibition of mitochondrial respiration (García-Ruiz et al., 2006). Fat-induced hepatic insulin resistance arises from excess lipid metabolites such as diacylglycerol-induced activation of PKC epsilon, which binds directly to and inhibits insulin receptor tyrosine kinase activity (Samuel et al., 2007). In this event, the primary defect is in mitochondrial fatty acid oxidation capacity, which leads to about 4-fold increase in diacylglcerol accumulation and PKC epsilon activation (Zhang et al., 2007). Apart from the decreased anti-oxidant capacity, patients suffering from hepatocellular dysfunction despite their increased mitochondrial mass, have diminished maximal respiration. Additionally, these cases have severe hepatic insulin resistance, mitochondrial uncoupling, and leaking activity (Koliaki et al., 2015).

4. Flavonoids-rich natural products and obesity-related insulin resistance

Polyphenols, as antioxidants are the most common ingredient of the diet that are found ample amounts, specifically in fruits, vegetables, cereals, dry legumes, chocolate, and beverages, such as tea, coffee, or wine (Scalbert et al., 2005). Pérez-Jiménez et al. created a list of the 100 richest dietary sources of polyphenols with contents ranging from 15,000 mg per 100 g in cloves to 10 mg per 100 ml of rosé wine. The sources with the higher content are various spices and dried herbs, cocoa products, some darkly colored berries, some seeds (flaxseed), nuts (chestnut, hazelnut) and some vegetables, including olive and globe artichoke heads. At least 89 foods and beverages providing more than 1 mg of total polyphenols per serving is established. (Pérez-Jiménez et al., 2010). Among others, some fruits like apples, grapes, pears, and berries typically contain high amounts of polyphenols with 200–300 mg per 100 g (Scalbert et al., 2005).

Compared to black tea, green tea contains the highest amount of catechins. Catechins are the primary polyphenols in green tea and constitute about 35% of its dry weight. A two-gram green tea bag contains approximately 500 mg of green tea catechins (Wang et al., 2014). Green tea catechins show a dose dependent suppressive effect on preadipocyte proliferation and adipocyte differentiation by down-regulating the expression of PPAR-gamma and C/EBP-alpha at the mRNA and protein levels (Chan et al., 2011). Even if catechin exhibits pro-oxidant effect in protein carbonyl formation at lower concentrations, its significant antioxidant effect occurs at higher concentrations. There is a balance between the anti-oxidant and pro-oxidant properties of catechins (Lu et al., 2011). Mitochondrial ROS are physiological activator of activated adenosine-monophosphate-activated protein kinase (AMPK) and that AMPK activation triggers a peroxisome proliferator-activated receptor-gamma coactivator-1alpha-dependent antioxidant response that limits mitochondrial ROS production. AMPK deficient cells exhibit elevated mitochondrial ROS levels, thereby undergo premature senescence (Rabinovitch et al., 2017). Catechins and capsaicin stimulate the mitochondrial ROS release, which activated AMPK. Thereby AMPK inhibits both adipocyte differentiation and apoptosis in mature adipocytes (Hwang et al., 2005). Concurrently, polyphenols modulate signaling pathways including the AMPK, PPAR-gamma, CCAAT/enhancer binding protein alpha, PPAR-gamma activator 1-alpha, sirtuin 1, sterol regulatory element binding protein-1c, uncoupling proteins (UCP) 1 and 2, and NF-kappaB that regulate adipogenesis, antioxidant and anti-inflammatory responses (Wang et al., 2014). Thus, epigallocatechin-3-O-gallate improves free fatty acids-induced peripheral insulin resistance. This might be dependent on decreasing oxidative stress, activating the AMPK pathway and regulating insulin signaling pathway by catechins (Li et al., 2011).

However, considering the dietary habits, there is a significant difference in the polyphenol intake within countries. As polyphenols originate from plants, compared to the individuals who have westernized diets, vegetarians and vegans are supposed to have greater intakes of polyphenols. However, in the US and Canada, coffee consumption has a much bigger influence on the quantity of total polyphenol intake than the dietary pattern itself (Chiva-Blanch and Badimon, 2017). Polyphenols may serve to act beneficially on the detrimental effects of insulin resistance and diabetes-related inflammation and oxidative stress (Scalbert et al., 2005). Actually, polyphenols are a large group of phytochemicals containing phenol rings and are divided into flavonoids, phenolic acids (virgin olive oil, red wine, walnuts, red raspberry), resveratrol (grapes, red wine and nuts) and lignans (virgin olive oil, rye flour and sesame seed oil) (Guasch-Ferré et al., 2017). Briefly, dietary polyphenols prevent obesity development through the following possible mechanisms: lower food intake; decrease lipogenesis; increase lipolysis; stimulate fatty acid beta-oxidation; inhibit adipocyte differentiation and growth; attenuate inflammatory responses and suppress oxidative stress; and improve insulin resistance (Wang et al., 2014). Flavonoids are naturally occurring phenolic compounds with a vast range of bioactivities. Approximately 4000 flavonoids have been discovered so far (Cook and Samman, 1996). Furthermore, flavonoids are classified into flavones (Virgin olive oil, oranges, whole grain wheat-flour bread), flavonols (Spinach, beans, onions), flavanols (Red wine, apples, peaches, cocoa powder, nuts, dark chocolate), flavanones (orange juice, grapefruit juice), isoflavonoids (Soy flour, roasted soy bean), and anthocyanins (Cherries, red wine, olives, hazelnuts, almonds, black elderberry, black chokeberry, blueberries) (Guasch-Ferré et al., 2017; Pérez-Jiménez et al., 2010). Gallic acid and isoflavones are the ones that are best absorbed, while catechins, flavanones, and quercetin glucosides follow them, but all of them have different kinetics. The least well-absorbed polyphenols are the proanthocyanidins, the galloylated tea catechins, and the anthocyanins (Manach et al., 2005).

The basic flavonoid structure consists of 15 carbon atoms, and three rings of which two are benzene rings connected with a 3-carbon chain (Croft, 1998). The study of follow-up of 7447 randomly assigned participants, over a mean of 5.51 years (18,900 person-years) revealed that a high total flavonoids intake, especially as flavanones and dihydroflavonols, is related with a diminished risk of diabetes in older adults. (Tresserra-Rimbau et al., 2016). Citrus plants are a considerable source of flavonoids, while naringin, naringenin, nobiletin, narinurtin, and
hesperidin are the most significant flavonoids that are isolated from the fruits of these plants (Tripoli et al., 2007). In general, citrus fruit extracts possess large amounts of flavonoids and show potent free radical scavenging activity (Guimaraes et al., 2010). Indeed, flavonoids are strong anti-inflammatory compounds. Naringin is the major flavonoid glycoside in grapefruit and gives grapefruit juice its bitter taste. Naringin exerts anti-inflammatory activity in addition to antioxidant activity and blood lipid-lowering effects. This flavonoid decreases the elevated TNF-alpha concentration and inflammatory cell accumulation (Jain and Parmar, 2011). Recent evidence suggests that naringin upregulates NAD(P)H:quinone oxidoreductase 1, heme oxygenase-1, glutathione S-transferase pi 1, and gamma-glutamylcysteine ligase mRNA expression followed by activation of nuclear factor erythroid 2-related factor 2 and decreases the expression of proinflammatory mediators such as TNF-alpha, cyclooxygenase-2 (COX-2), and iNOS (Gopinath and Sudhandiran, 2012). Naringin and naringenin both are potent free radical scavengers, thus take part in the prevention of lipid peroxidation. Flavonoids scavenge bothsuperoxide and hydroxyl radicals in vitro (Cavia-Saiz et al., 2010). Xanthine oxidase enzymes are physiologic sources of superoxide anions in eukaryotic cells. Naringin was shown to be a significant inhibitor of xanthine oxidase activity, in vitro (Russo et al., 2000). It also exhibited strong antioxidant activity, in vivo, in different disease conditions. A protective effect of naringin was detected in diabetic subjects. Furthermore, naringin supplementation improves antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase in diabetic animals (Ali and El Kader, 2004; Punithavathi et al., 2008). The daily mean intake of flavonoids has been found to be from tea (157 mg), citrus fruit juices (8 mg), wine (4 mg), and citrus fruits (3 mg) (Alam et al., 2014). A higher consumption of anthocyanins and anthocyanin-rich fruit was associated with a lower risk of type 2 diabetes (T2D) (Wedick et al., 2012). Thus, anthocyanin-rich foods decrease insulin and inflammation levels. Although, no significant associations are found with total or other flavonoid subclasses, higher intakes of both anthocyanins and flavones ameliorate insulin resistance (Jennings et al., 2014). Nuts, and red wine consumption have been determined to be inversely correlated with insulin resistance and T2D. To some extent, these associations may be related with the high levels of polyphenols and bioactive compounds intake with these traditional dietary habits (Guauch-Ferré et al., 2017). It has been recognized that in course of obesity as a result of high-fat diet, lemon polyphenols considerably suppressed body weight gain, fat accumulation, and the development of hyperlipidemia, hyperglycemia, and insulin resistance. These effects of lemon polyphenols are attributed to their upregulation of mRNA levels of the enzymes involving in beta-oxidation. In this context, PPAR-alpha, acyl-CoA oxidase, fatty acid synthase activities increase in liver and white adipose tissue (Fukuchi et al., 2008).

From the clinical standpoint, insulin resistance and endothelial dysfunction are the key mediators in the pathogenesis of atherosclerosis. Endothelial dysfunction is an inevitable outcome of the metabolic or insulin resistance syndrome. Presence of inadequate amounts of endothelium-derived nitric oxide (NO) is the component that associates insulin resistance with endothelial dysfunction (Cersosimo and DeFronzo, 2006). One of the potential mechanisms of oxidative stress is through the activation of NADPH oxidase by lipid accumulation in the adipocyte, and resultant increased ROS production (Furukawa et al., 2004). In fact, NADPH oxidase is a major source of superoxide in cardiovascular cells, and oxidative stress can be involved in the process of endothelial dysfunction. NADPH oxidase can be activated in hyperglycemia through the PK C pathway, secondary to lipid accumulation (Nakagami et al., 2005). Once activated these enzymes produce ROS and other radicals that can modify NO availability (Carr et al., 2000). Peroxynitrite formed in vivo from superoxide and NO can mediate oxidative nitration or nitrosation reactions, leading to tissue injury. Consequently, reduction in NO may be due to the formation of peroxynitrite and other reactive nitrogen species (RNS) (Engin, 2011; Engin et al., 2015). Following the ethanolic-induced oxidative stress, treatment with flavanol-rich cocoa liquor has been presented to trigger NO synthesis and to significantly decrease the activation of xanthine oxidase and myeloperoxidase (Osakabe et al., 1998). Cocoa and chocolate have varying concentrations of flavonoids. In fact, flavanol-rich, plant-derived foods and beverages include wine, tea, and various fruits and berries, as well as cocoa and cocoa products. Flavanols are present as either the monomers of epicatechin and catechin or oligomers of epicatechin and/or catechin (procyanidins) in these flavonoids (Adamson et al., 1999). Steinberg et al. indicated that flavan-3-ols and their oligomeric derivatives, procyanidins are the main flavonoids of cocoa. These compounds present various range of beneficial effects like antioxidant protection and modulation of vascular homeostasis (Steinberg et al., 2003). Several molecular targets, such as NF-kappaB, endothelial nitric oxide synthase (eNOS), angiotensin-converting enzyme, have been identified, which may partly explain potential beneficial cardiovascular effects of cocoa polyphenols (Rimbach et al., 2009). In addition, some forms of cocoa and chocolate rich in flavonoids, may have the potential effects to improve insulin resistance (Kris-Etherton and Keen, 2002). Thus, Shrime et al. showed that flavonoid-rich cocoa consumption significantly improved blood pressure, insulin resistance and lipid profiles in 1106 individuals. In this study, the effects of cocoa intake on insulin sensitivity was determined after 2–18 weeks (Shrime et al., 2011). Indeed, cocoa intake can prevent high-fat diet-induced obesity by diminishing fatty acid synthesis and fatty acid transport. Additionally, cocoa intake decreases the expression of genes that synthesize fatty acid transport-relating molecules, while it upregulates the expression of genes for thermogenesis (Matsui et al., 2005). However, consumption of flavanol-rich cocoa for four days, has been shown to induce consistent and remarkable peripheral vasodilation via activation of the NO system. The beneficial effect of flavanoll-rich cocoa on endothelial functions could be observed in earlier period in comparison to insulin sensitivity (Fishier et al., 2005). Over the past years, the presence of flavanol receptors, which activate the intracellular signaling pathways has been debated. Recently, Moreno-Ulloa et al., 2014 showed that the flavanol, (-)-epicatechin stimulates NO production via Ca2+-independent eNOS activation. Indeed, under Ca2+ free conditions, the signaling pathway leads to eNOS activation via (-)-epicatechin cell membrane receptor mediating eNOS activity (Moreno-Ulloa et al., 2014). Mechanistically, (-)-epicatechin interacts with the same binding site and shares similar molecular recognition properties to those observed for G1 at the G protein-coupled estrogen receptor (GPER). GPERs are at the cell-surface and co-localize with cytoskeletal structures on F-actin filaments (Moreno-Ulloa et al., 2015) (Fig. 1). Long-term dietary consumption of cocoa flavanol oligomers is the most efficient strategy in preventing weight gain, fat mass enhancement, impaired glucose tolerance, and insulin resistance (Dorenkott et al., 2014). Compared to low-flavanol cocoa, high-flavanol cocoa improves endothelial functions immediately, whereas insulin resistance may be reduced over a 12-weeks period (Davison et al., 2008). Furthermore, sugar-free cocoa ingestion ameliorates endothelial function more effectively, compared to placebo and sugar-sweetened cocoa (Njike et al., 2011). After the acute consumption of cocoa, the improvements in endothelial function observed with the consumption of sugar-free cocoa are significantly greater than those seen with sugared cocoa. Although both sugar-sweetened cocoa and sugar-free cocoa contains 3282 mg polyphenols and the antioxidant composition of the two cocus are the same, more significant effects of sugar-free cocoa can be related with the lack of the sugar (Faridi et al., 2008). Moreover, acute feeding studies showed that, flavanol-rich cocoa and chocolate increases plasma antioxidant capacity and reduced platelet reactivity (Kris-etherton and Keen, 2002). After human subjects drank a cocoa beverage with an ingredient of epicatechin to catechin in a 1:1 ratio, peak plasma catechin concentrations reached up to 10% of the peak epicatechin concentrations (Holt et al., 2002). Monomeric cocoa catechins improve the cellular redox state. Therefore, migration of Nrf2
into the nucleus is stimulated, the key genes for the mitochondrial respiration are up-regulated, glucose-stimulated insulin secretion is increased, and as a result, beta-cell function is improved (Rowley et al., 2017). One of the target cells of epicatechin is macrophage. Epicatechin supplemented high fat diet protects from diet-induced obesity and insulin resistance. The beneficial effects of this polyphenol could be mediated by marked suppression of chemokine (CC motif) ligand 19 expression (Sano et al., 2017). While cocoa flavanols and procyanidins can suppress the production of the proinflammatory cytokines, such as IL-1beta, IL-2 and 15- lipoxigenase activity, they enhance the production of the anti-inflammatory cytokine, IL-4 in peripheral blood mononuclear cells (Mao et al., 2000a, 2000b; Sanbongi et al., 1997; Schewe et al., 2001). These flavonoids beneficially modulate transforming growth factor-beta1 (TGF-beta1) and TNF-concentrations in blood mononuclear cells (Mao et al., 2002). Epicatechin, catechin, and an isolated fraction of B-type dimers (B2 and B5) are shown to regulate NF-kappaB (Mackenzie et al., 2004). Likewise, procyanidins have been observed to modulate the expression of the NF-kappa B-dependent IL-2 and IL-1beta (Mao et al., 2000a; Sanbongi et al., 1997). Thus, insulin-stimulated Akt phosphorylation is considerably increased; pro-inflammatory cytokine expressions are remarkably diminished, and JNK phosphorylation is downregulated in the liver of those animals that are treated with apple procyanidins (Ogura et al., 2016).

Insulin resistance is a cause, at least partly, of endothelial dysfunction. Therefore, while cocoa and its flavonoids improve endothelial dysfunction, Grassi et al., 2013 suggested that flavonoids also provide a beneficial effect on insulin resistance (Grassi et al., 2013). However, West et al., found that the blood insulin levels and insulin resistance did not differ in between the groups consuming either low-flavanol or high-flavanol cocoa + dark chocolate. Furthermore, the cocoa + dark chocolate intake has no effect on fasting blood measures. The high-flavanol cocoa and dark chocolate treatment enhance vascular reactivity, causing vasodilation and significant reductions in arterial stiffness in women (West et al., 2014). Similar to high-flavanol cocoa, chocolate flavanols stimulate the elevation of NO bioavailability, thus, guard the vascular endothelium, and diminish cardiovascular disease risk factors. Flavanol-rich dark chocolate has stronger positive impact than the flavanol-free white chocolate (Grassi et al., 2008). In this respect, when the effects of dark chocolate on endothelial function, insulin sensitivity, beta-cell function, and blood pressure are compared with the white chocolate, (Grassi et al., 2008), the beneficial influences of flavonoids are attributed to their natural antioxidant properties, and their ability to improve the NOS activity (Fisher et al., 2003; Karim et al., 2000). Thus, flavanol-rich dark chocolate ameliorates insulin sensitivity in hypertensive subjects (Grassi et al., 2005).

The amounts of cocoa and chocolate required to correct various obesity-related complications have been determined by multiple studies. Both flavanol-rich cocoa and chocolate elevate plasma antioxidant capacity and decrease platelet response. Flavanon-rich chocolate generates acute and chronic effects when it is consumed 38 and 125 g, respectively. Approximately 150 mg of flavonoids are required to initiate a rapid antioxidant action and to change the prostanoylcs levels. Some dose-response studies revealed that an antioxidant effect occurs with approximately 500 mg flavonoids (Kris-Etherton and Keen, 2002). Randomized controlled trials comprised 1297 participants showed that insulin resistance, homeostatic model assessment-insulin resistance (HOMA-IR), is improved by chocolate or cocoa due to significant decreases in serum insulin. In this study, total flavonoid intake ranged from 16.6 mg/day to 1080 mg/day and control group consumed low-flavanoid cocoa (Hooper et al., 2012). 1.7 g/day of total chocolate (24% of intake from dark chocolate) was associated with lower systolic and diastolic blood pressure and a 10% lower 8-year risk of stroke (Buijss et al., 2010). In patients who had myocardial infarction before, consuming chocolate twice a week compared to never consuming chocolate was also associated with a 66% decrease in 8-year cardiac mortality (Janszky et al., 2009). Improvements in HOMA-IR was observed after twice-daily consumption of cocoa drinks containing 19, 22, or 54 g cocoa/day; 46 or 100 g dark chocolate/day; or 48 g chocolate plus 18 g cocoa/day (Buijss et al., 2006). Curtis et al., 2012 compared the flavonoid-rich cocoa drinks, dark or milk chocolate, cocoa supplements, solid chocolate plus cocoa drinks, cocoa powder and chocolate with the low flavan-3-ol versions of the same foods in a randomized, placebo-controlled trial. The intake of 27 g/day flavonoid-enriched chocolate, which contains 850 mg flavan-3-ols and 100 mg isoflavones for 1 year, significantly improved peripheral insulin resistance (Curtis et al., 2012). In a double-blinded 6-week clinical trial involving 32 obese nondiabetic individuals, intake of blueberry, which contains 668 mg/day anthocyanin significantly increased insulin sensitivity without significant changes in adiposity and inflammatory biomarkers (Stull et al., 2010). Beneficial effects of anthocyanins on improving insulin resistance were also observed in a 12-week trial conducted in 74 patients with nonalcoholic fatty liver disease (Zhang et al., 2015). Intake of flavan-3-ols and their food origins have showed overall positive influences on diminishing insulin resistance, chronic systemic inflammation and oxidative stress (Guasch-Ferré et al., 2017).

Instant, espresso, filter and Turkish/Greek coffee brews, coffee substitutes and individual compounds contain phenolic acids, flavonoids, methylxanthines, N-methyl pyridinum and HMW melanoids. Antioxidant activity of coffee is ascribed to methylxanthines and N-methyl pyridinum residues. The highest values of the relative antioxidant capacity index are attributed to instant coffee brews, while the lowest to the decaffeinated espresso coffee (Gorjanović et al., 2017). The most common phenolic acids are caffeic acid and ferulic acid, which are major phenolic compounds in coffee and cereals, respectively (Manach et al., 2004). The volatile compounds present in the ground, roasted coffee beans are responsible for the unique aroma of the coffee smell. On the other hand, the alkaloids caffeine and trigonelline, chlorogenic acids (a polyphenol that occurs in large amounts in coffee), the diterpenes cafestol and kahweol, and melanoids, the Maillard reaction products, are produced during the gramming and roasting process and together with the volatile ingredients constitute the key composition of the coffee beverage (Ludwig et al., 2014). Green coffee is a substantial source of polyphenols and methylxanthines, and represent high antioxidant capacity. Thus, thirty-eight polyphenols and two methylxanthines derivatives are identified in Arabica green coffee beans. Among all the compounds, caffeoylquinic acid is the amolest one, (up to 85.5%) followed by dicaffeoylquinic and feruloylquinic acids (up to 8 and 7%, respectively) and the recently identified cinnamoyl-glycerides (up to 2.5%). Caffeine is the main methylxanthine (99.8%) source, with minimal concentrations of theobromine (0.2%). African coffees (from Kenya and Ethiopia) have greater polyphenolic content than American beans (from Brazil and Colombia), while methylxanthine contents differ randomly (Baæa et al., 2016). Colombian coffee extract has high levels of caffeine and diterpenoids. Usually, 7–8 g coffee is required to make a cup of coffee. The daily dose of coffee consumption corresponding to approximately 4–5 cups/day of coffee was used in a study of Wistar rats. This amount of coffee extract attenuated the impairment in glucose homeostasis without altering the adipobul fat deposition and plasma lipid profile in diet-induced obesity (Panchal et al., 2012). Moderate daily caffeine consumption, up to 400 mg/day, that is equivalent to 6 mg/kg body weight/day considering a 65-kg person, is not connected with adverse effects. Plasma caffeine concentration reaches maximum levels within 60–90 min after the ingestion (Nawrot et al., 2003).

When green coffee is roasted at high temperatures, Maillard reactions create a number of unique compounds. Roasting results in some part of the antioxidant, chlorogenic acid, to be converted into quinides, which are suggested to alter the blood glucose concentrations (Tunnicliffe and Shearer, 2008).

Furthermore, coffee consumption supports the improvement of the pancreatic beta-cell damage and steatohepatitis, to different levels (Watanabe et al., 2017). Long-term caffeine intake can help to alleviate
diabetic symptoms by enhancing insulin sensitivity and beta-cell function through improved insulin/insulin-like growth factor-1 (IGF-1) signaling via induction of IRS-2 (Park et al., 2007). While circulating levels of adiponectin increase after a long-term coffee consumption, plasma leptin levels decreases. Coffee consumption shows beneficial metabolic effects by improving adipocyte functions and decreasing insulin resistance (Lee et al., 2017). On the one hand, circulating high adiponectin downregulates the obesity-linked insulin resistance via its receptors, which mediate the antidiabetic metabolic actions of adiponectin (Kadowaki et al., 2006). On the other hand, leptin is secreted from fat proportionally depending on the degree of adiposity. It is transported across the blood-brain barrier, and functions in the brain to diminish appetite and increase thermogenesis. By this way, ultimately decreases adiposity. Contrarily, in obesity, higher levels of circulating leptin fail to reduce adiposity because of the leptin resistance arise. In fact, the blood-brain barrier transporter is the initial step in the failure of the feedback loop (Banks, 2008).

Recently, coffee has been recognized as a beneficial beverage for healthy aging. Regular coffee intake augments the energy expenditure and the respiration exchange ratio. In habitual coffee drinkers, the mammalian target of rapamycin (mTOR) complex 1 (mTORC1) is inhibited and the nocturnal locomotor activity increases without disrupting the circadian rhythm (Takahashi and Ishigami, 2017). Aged rats exhibit diminished insulin sensitivity, which is accompanied by hyperinsulinemia and normoglycemia. The other accompanying findings in these subjects are increased visceral and total fat, decreased total antioxidant capacity and plasma catecholamines, and also decreased skeletal muscle glucose transporter 4 (GLUT4) and AMPK protein expression. Chronic caffeine intake restores insulin sensitivity and regularizes circulating insulin and non-esterified fatty acids in aging (Guarino et al., 2013). Long-term caffeine consumption prevents the development of insulin resistance and hypertension in the high-fat models and that this effect is connected with the decline of the catecholamines in the circulation. In the high-fat-fed animals, caffeine administration restores fasting insulin concentrations to control ranges and reverses enhanced weight gain and visceral fat mass (Conde et al., 2012). Catechin-polyphenols and caffeine of the green tea extract efficiently induce thermogenesis by relieving the inhibition at several control points along the noradrenaline-cyclic AMP (cAMP) axis (Dulloo et al., 2000). Indeed, the sympathetic nervous system is involved in the regulation of energy balance and breakdown of lipids to glycerol and free fatty acids. Caffeine has beneficial effects on the weight maintenance via supporting the thermogenesis and fat oxidation (Harpaz et al., 2017).

Roasting intensity alters the metabolic efficacy of coffee consumption. Dark roasted coffee intake improves post-load glucose metabolism by stimulating, thereby elevating the incretin and insulin secretions. In addition, dark roasted coffee in comparison to the light roasted coffee also enhances redox balance and increases omega-3 fatty acids (Di Girolamo et al., 2016). Although brewed coffee and espresso coffee have different and unique aroma profiles, the variations in the procedures of coffee preparation lead to the alterations in the chlorogenic acids and caffeine content (Caprioli et al., 2015). The combination of a temperature of 92 °C and pressure at 7 or 9 bar seems to be the ideal setting for the most efficient extraction of caffeine, trigonelline and nicotinic acid and for their resultant consumption, as well. The compound extracted in the greatest quantity is caffeine, which is in the range of 116.87–199.68 mg in a 25 ml cup of coffee (Caprioli et al., 2014). Either light or dark roasted coffees that contain different chlorogenic acid, during oral glucose tolerance test, do not affect the glucose or insulin responses distinctively, but both raise the insulin response compared to water (Rakvaag and Dragsted, 2016). It has been indicated that superoxide phosphorylates IRS1 at serine 307 causing a diminished IRS1-insulin receptor interaction and suppression of the activity of PI3K (Bloch-Dami et al., 2006; Boura-Halfon and Zick, 2009). This leads to the inhibition of insulin signaling (Boura-Halfon and Zick, 2009). Furthermore, NADPH oxidase is activated by advanced glycation end products that may lead to the generation of superoxide radicals, alter receptor for advanced glycosylation end products (RAGE) and impaired NO bioavailability (Wautier et al., 2001). Yeh et al., 2014 showed that central insulin resistance may be associated with superoxide-dependent pathway due to the impaired NO synthesis and resultant hypertension. However, caffeine may inhibit the superoxide production related to the RAGE-mediated NADPH oxidase, as well as stimulating NO synthesis (Yeh et al., 2014). Insulin-PI3K-Akt-nNOS signaling is linked to NO production and blood pressure regulation. Caffeine may reverse the defect in the insulin signaling pathway to increase NO production and to decrease blood pressure by upregulating IRS-1-PI3K-Akt-neuronal NOS signaling and abolishing the superoxide production (Yeh et al., 2014).

In contrast, acute caffeine intake reduces insulin sensitivity in a concentration dependent manner. Insulin resistance induced effect of caffeine is mediated by A1 and A2B adenosine receptors. Both GLUT4 and NO seem to be downstream effectors involved in insulin resistance induced by acute caffeine ingestion (Beaudoin et al., 2013; Sacramento et al., 2015). The meta-analysis of 22 eligible randomized controlled trials with 1584 subjects showed that the administration of green tea catechins with or without caffeine results in a significant reduction in fasting blood glucose, whereas fasting blood insulin and HOMA-IR is unchanged (Zheng et al., 2013).

The antioxidant effects of flavonoids in tea attenuates the inflammatory reactions in atherosclerosis, by decreasing thrombosis, supporting the normal endothelial function, and preventing the expression of cellular adhesion molecules (Kris-Etherton and Keen, 2002). Commonly, in the brewed tea around 172 mg total flavonoids per 255 ml (brewed for 2 min) can be found; for this reason, intake of 1 and 3.5 cups of tea would be expected to bring out acute and chronic physiologic impacts, respectively (Kris-Etherton and Keen, 2002). The infusions of green tea have around 2.5-fold greater antioxidant capacity than black tea’s. During the infusion procedure, both green and black teas release remarkable amounts of antioxidants into the hot water within 2 min (Langley-Evans, 2000). Caffeine concentrations in white, green, and black teas ranged from 14 to 61 mg per serving. The decaffeinated teas contained less than 12 mg of caffeine per serving (Chin et al., 2008). All beneficial effects of the black tea, including the antioxidant potential have been shown to be completely inhibited by the addition of milk to tea. Of the various kinds of milk proteins, the caseins cause these inhibiting effects of milk via formation of complexes with tea catechins (Langley-Evans, 2000; Lorenz et al., 2007). During the last years, there has been growing scientific interest in potential health benefits of polyphenols in insulin resistance-related diseases. Moreover, the role of polyphenols in the prevention and treatment of human obesity-related chronic diseases such as cardiovascular disorders and diabetes mellitus are needed to be further investigated (Costa et al., 2017).

5. Conclusion

Although many beneficial effects are ascribed to flavonoids improving obesity-related complications, their preventive effect on obesity-related insulin resistance has been less known. Recent evidences show that polyphenol intake can prevent high-fat diet-induced insulin resistance via cell surface GPERs by upregulating the expression of related genes, and their pathways, which are responsible for the insulin sensitivity.

Author disclosure statement

All authors disclose that they have no conflict of interest.