Vascular Pharmacology 58 (2013) 3–20

Contents lists available at SciVerse ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

Phytochemicals and their impact on adipose tissue inflammation and diabetes

Andreas Leiherer [a,c,d], Axel Mündlein [a,c], Heinz Drexel [a,b,c,e,*]

[a] Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Feldkirch, Austria
[b] Department of Medicine and Cardiology, Academic Teaching Hospital Feldkirch, Feldkirch, Austria
[c] Private University of the Principality of Liechtenstein, Triesen, Liechtenstein
[d] Medical Central Laboratories, Feldkirch, Austria
[e] Drexel University College of Medicine, Philadelphia, USA

ARTICLE INFO

Article history:
Received 26 March 2012
Received in revised form 3 September 2012
Accepted 4 September 2012

Keywords:
adipocytes
inflammation
diabetes
Western diet
resveratrol

ABSTRACT

Type 2 diabetes mellitus is an inflammatory disease and the mechanisms that underlie this disease, although still incompletely understood, take place in the adipose tissue of obese subjects. Concurrently, the prevalence of obesity caused by Western diet's excessive energy intake and the lack of exercise escalates, and is believed to be causative for the chronic inflammatory state in adipose tissue. Overnutrition itself as an overload of energy may induce the adipocytes to secrete chemokines activating and attracting immune cells to adipose tissue. But also inflammation-mediating food ingredients like saturated fatty acids are believed to directly initiate the inflammatory cascade. In addition, hypoxia in adipose tissue as a direct consequence of obesity, and its effect on gene expression in adipocytes and surrounding cells in fat tissue of obese subjects appears to play a central role in this inflammatory response too.

In contrast, revisiting diet all over the world, there are also some natural food products and beverages which are associated with curative effects on human health. Several natural compounds known as spices such as curcumin, capsaicin, and gingerol, or secondary plant metabolites catechin, resveratrol, genistein, and quercetin have been reported to provide an improved health status to their consumers, especially with regard to diabetes, and therefore have been investigated for their anti-inflammatory effect. In this review, we will give an overview about these phytochemicals and their role to interfere with inflammatory cascades in adipose tissue and their potential for fighting against inflammatory diseases like diabetes as investigated in vivo.

Contents

* Corresponding author at: Vorarlberg Institute for Vascular Investigation and Treatment (VIVIT), Carinagasse 47, 6800 Feldkirch, Austria. Tel.: +43 5522 303 2600; fax: +43 5522 303 7533.
E-mail address: vivit@lkhf.at (H. Drexel).

1537-1891/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.vph.2012.09.002

1. Introduction

1.1. Cellular interplay

Obesity and insulin resistance in patients suffering from type 2 diabetes mellitus (T2DM) are associated with a chronic low-grade systemic inflammation, characterized by an increased expression of inflammatory markers (Capurso and Capurso, 2012). The main origin of this inflammatory response is the adipose tissue. In general, there are two types of adipose tissue in mammals; white adipose tissue storing energy as triglycerides and brown adipose tissue producing heat from fat stores. They differ from each other by their morphology and metabolic function, their presence and distribution, and also by their origin. However, in human adults, brown adipose tissue has been long considered to be absent or at least of no relevance. As data addressing effects of natural compounds on brown fat tissue are rather limited, white adipocytes are referred to just as adipocytes in the following.

Apart from energy storage, adipocytes also produce cytokines including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1 (Mcp-1), leptin, adiponectin and many other molecules, thereby referred to as adipokines. In the context of inflammation, the adipose tissue is infiltrated by macrophages, also releasing pro-inflammatory mediators (e.g. TNF-α; IL-6; monocyte chemoattractant protein-1, MCP-1), producing reactive oxygen species (ROS) and inducing T-cell responses for successful defense against invading organisms (reviewed in Zeyda and Stulnig, 2007). In addition, also other immune cells like T-cells, natural killer T-cells, mast cells, and eosinophils are known to invade adipose tissue (Wu et al., 2007; Rausch et al., 2008; Rocha et al., 2008; Kintscher et al., 2008; Liu et al., 2009; Nishimura et al., 2009; Ohmura et al., 2010). Once present in adipose tissue, the interaction and crosstalk of immune cells with adjacent adipocytes amplify the inflammation. Importantly, these cells may also be directly induced to express pro-inflammatory genes by hypoxia (Burke et al., 2003).

1.2. Hypoxia

Obesity is characterized by tissue mass expansion creating areas of low O_2 pressure, as growing tissue can expand faster than the vasculature that supports it with oxygen (Virtanen et al., 2002; Kabon et al., 2004; Fleischmann et al., 2005; Pasarica et al., 2009). Mitochondria, as the oxygen-sensing machines in the cell, elevate their ROS production due to hypoxia (Klimova and Chandel, 2008) and, consequently, compensatory angiogenesis is induced. This leads to a reduction of adiponectin expression and secretion and an increase of pro-angiogenic genes including leptin, IL-6, and the vascular endothelial growth factor (VEGF) by adipocytes (Wang et al., 2007) and an induced expression of IL1β, IL-6 and TNF-α in macrophages (Ye et al., 2007). Therefore, hypoxia is another key-player with the potential to activate such inflammatory cascades in adipose tissue. Evidence for this hypothesis was provided previously when it could be demonstrated that hypoxia occurs in the adipose tissue of different obese mouse models and thereby contributes to the endocrine dysregulation (Hosogai et al., 2007; Ye et al., 2007; Rausch et al., 2008). However, it is unclear if hypoxia in adipocytes may trigger the inflammatory cascade per se without interference with immune cells or other parameters.

Hypoxia-inducible factor 1 (HIF-1) is known as the most important mediator of the hypoxic signal which is able to induce inflammation in the adipose tissue (Halberg et al., 2009). It is composed of two subunits, HIF-1α and HIF-1β, whereby the ß-unit is constitutively expressed and the α-subunit is regulated by O_2 at a post-translational level. HIF-1α is highly labile under normal oxygen conditions, but hypoxia strongly stabilizes HIF-1α as ROS prevent its hydroxylation and inhibit the subsequent rapid degradation by the proteasome (Fandrey et al., 2006; Klimova and Chandel, 2008). In a study of Regazzetti et al. (2009) it was observed that hypoxia causes a state of insulin resistance by decreasing insulin signaling pathways and inhibiting glucose transport in adipocytes and that this effect is triggered by HIF-1. In human adipocytes, hypoxia regulates the expression of adipokines like adiponectin, leptin, apelin, IL-6, plasminogen activator inhibitor-1 (PAI-1) angiopoietin-like protein 4 (ANGPTL4) and various other genes, which are involved in biological functions such as angiogenesis, inflammation, and energy metabolism (Wang et al., 2007, 2008; Gonzalez-Muniesa et al., 2011; Famulla et al., 2011; Wood et al., 2011; Geiger et al., 2011a, 2011b). Besides HIF-1, the hypoxic response can be mediated also by other transcription factors like nuclear factor-kappa B (NF-κB), c-Fos and activating transcription factor (ATF; Erickson and Millhorn, 1994; Prabhakar et al., 1995; Haxhiu et al., 1995; Cummins and Taylor, 2005; Chen et al., 2008).

1.3. Nutrition

The Western diet is characterized by an enhanced intake of fat and a decreased intake of plant extracts (Simopoulos, 2008) as well as an increased intake of energy and decreased energy expenditure (Eaton and Konner, 1985). Thus, one may hypothesize that adipocytes sense an overload of energy caused by overnutrition and respond by secreting chemokines recruiting pro-inflammatory macrophages to the adipose tissue. On the other hand, it is also possible that the nutrition itself, e.g. by pro-inflammatory fatty acids directly triggers the inflammation or counteracts this cascade by anti-inflammatory compounds. Regarding fatty acids, saturated fatty acids are a significant risk factor for developing T2DM (Ebbesson et al., 2010) whereas ω-3 fatty acids can be anti-inflammatory (Fig. 1; Lee et al., 2003a; Calder, 2005; Shi et al., 2006; Solinas et al., 2007; Oh et al., 2010; Lichtenstein et al., 2010), positively affecting insulin sensitivity and glucose tolerance (Dyerberg and Schmidt, 1989; Ebbesson et al., 2005; Jorgensen et al., 2006). A further hint for protective effect of some nutrients was given by the French paradox. This term describes the observation that people in France more seldom suffer from cardiovascular diseases despite their “unhealthy” diet, which is relatively rich in fat and alcohol in the form of red wine. Some polyphenols like resveratrol, quercetin and catechins are present at higher concentrations in red wines, especially in those from areas of southwestern France and Sardinia, because their traditional production methods ensure that these compounds are efficiently extracted from grapes. Indeed there is a correlation between these compounds in red wine from these areas and the longevity of their population (Corder et al., 2006).

The balance of consumed versus stored energy, represented by the AMP:ATP ratio, can be assessed by the AMP-activated protein kinase (AMPK). AMPK plays a central role in the regulation of glucose and lipid metabolism. Upon its activation by high AMP and low ATP levels, respectively, it increases cellular energy levels by inhibiting anabolic energy consuming pathways (synthesis of lipids, glucose and protein) and stimulating energy producing, catabolic pathways (e.g., the uptake and oxidation of glucose and fat). Therefore, this intracellular energy sensor up-regulates the glucose transporter GLUT4, which enhances glucose uptake, stimulates glycolysis and fatty acid oxidation and increases insulin sensitivity. Due to these functions, AMPK is a target for medical intervention in T2DM namely by the anti-diabetic drugs metformin and the adenosine analog 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR). Of interest, AMPK is also activated by hypoxia, glucose deprivation, leptin, adiponectin, and several phytochemicals (Hardie, 2011) and is a central inhibitor of inflammatory function (reviewed in Salminen et al., 2011).

1.4. Inflammatory pathways

Glitazones are one of the most common groups of medications used for the treatment of T2DM acting via the activation of

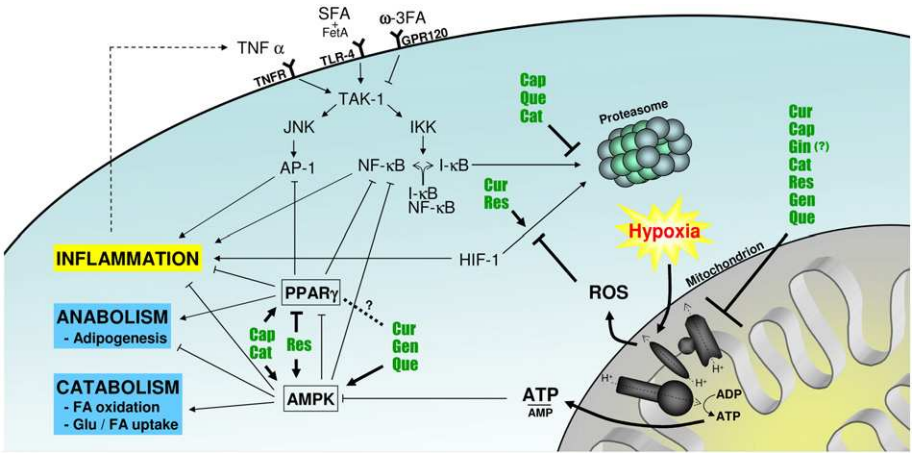

Fig. 1. Schematic representation of phytochemicals' targets. The model gives an overview about the major interfering points of phytochemicals on cellular inflammatory pathways as described in the text. Hypoxia is sensed at the mitochondrial electron transport chain and elicits production of reactive oxygen species (ROS), preventing HIF-1 hydroxylation and proteasomal degradation. Further inflammatory mediators like tumor necrosis factor (TNF) α or saturated fatty acids (SFA) are able to induce or, in the case of anti-inflammatory ω3-fatty acids (FA), to inhibit activation of JNK and IKK-signaling cascades via TAK-1. Thus HIF-1, AP-1 and NF-κB are activated for triggering expression of pro-inflammatory genes. The master regulator for cellular metabolism AMP-activated kinase (AMPK) induces catabolic and inhibits anabolic cascades upon its activation by cellular energy shortage, represented by a high AMP level but also impacts inflammation. The phytochemicals (green) interfere with these pathways by inhibiting inflammatory pathways and affecting metabolism, which finally accounts for their anti-diabetic effect. Although some of their reviewed properties and the underlying cellular mechanisms are still not elucidated in detail, a majority of their effects may be explained by interference with the mitochondrial located electron transfer chain and the coupled oxidative phosphorylation generating ATP. The abbreviation Cap denotes capsaicin, Cat catechins, Cur curcumin, FetA fetuin-A, Gen genistein, Gin gingerol, Glu Glucose, GPR120 G protein-coupled receptor 120, Que quercetin, Res resveratrol, TAK-1 transforming growth factor-β activated kinase 1.

peroxisome proliferator-activated receptor (PPAR) γ. PPARs are on the one hand master regulators of metabolism but on the other hand also regulate inflammatory processes. In general, they all have anti-inflammatory activities. PPARγ is restricted largely to adipose tissue, and also to immune cells, but to a much lesser extent. It is an activator of adipogenesis as it induces fatty acid synthesis and storage and therefore it is likely inhibited by AMPK (Panunti and Fonseca, 2006; Lee et al., 2009b; Sozio et al., 2011). In addition, PPARγ represses expression of inflammatory genes like inducible nitric oxide synthase (iNOS), inhibits transcription factors AP-1 and NF-κB, modulates mitogen-activated protein kinase (MAPK) activity and influences glucose uptake (reviewed in Varga et al., 2011). Therefore, PPARγ is a suitable target for medical intervention, and PPARγ-activating pioglitazone is a well known anti-diabetic drug for treatment of T2DM (Fig. 1).

The activator protein 1 (AP-1), which is recognized as a target of PPARγ and of many other anti-inflammatory compounds, is involved in the regulation of inflammatory responses (Matthews et al., 2007). It is a dimeric transcription factor complex with a broad combinatorial possibility of transcription factors mainly from the Jun, Fos and ATF families. c-Jun e.g. is a proto-oncogene playing a role in the development of many cancers, but also in insulin resistance (Thompson et al., 1996). It is phosphorylated by the c-Jun amino-terminal kinase (JNK), whereby its transcriptional activation is enhanced (Fig. 1; Vogt, 2001).

The inflammation- and stress-induced kinases JNK and IκB kinase-β (IKKβ) are central signal transducers in innate immunity and stress responses that control the expression of several pro-inflammatory genes. Of interest, both kinases represent a link between inflammation and insulin resistance, as they are activated by factors known to promote insulin resistance, and T2DM too. JNK is a member of the MAPK family, phosphorylating and activating transcription factors including ELK-1, ATF, and JUN (reviewed in Davis, 2000; Kyriakis and Avruch, 2001). IKKβ, on the other hand, is responsible for activation of NF-κB. It phosphorylates the inhibitor IκBα protein, which results in its ubiquitination and dissociation from NF-κB (Fig. 1). Thereby, NF-κB becomes activated and enters the nucleus and regulates transcription of genes involved in innate immunity and inflammation. One important downstream target of NF-κB is cyclooxygenase-2 (COX-2), which catalyzes the production of prostaglandins (e.g. prostaglandin E2; PGE_2), the key molecules in pain and inflammation processes of the body. Hence, COX-2 inhibitors like non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit the prostaglandin production, are among the most commonly used medications. A second target of NF-κB, iNOS, is involved in immune response, producing large amounts of nitric oxide as a defense mechanism. NF-κB also induces expression of cytokines TNF-α, IL-6, IL-1β and many other genes (reviewed in Yamamoto and Gaynor, 2001). Thereby NF-κB is involved in a feed-forward regulation, as some of these pro-inflammatory cytokines, produced in response to NF-κB activation, can activate JNK and NF-κB again (reviewed in Solinas and Karin, 2010; Donath and Shoelson, 2011). Moreover, also extracellular stimuli like free fatty acids, in particular the saturated fatty acid palmitic acid, are able to bind not only to surface receptors Toll-like receptors (TLR) 2 and 4, present on immune cells, but also on adipocytes (Bès-Houtmann et al., 2007), to activate both these pathways (Fig. 1; Shi et al., 2006; Senn, 2006; Kawai and Akira, 2007; Nguyen et al., 2007). Recently, fetuin-A has been identified as an adaptor which binds to saturated fatty acids as well as TLR4 thus mediating TLR signaling in adipocytes (Pal et al., 2012 582/id). A similar effect is shown for advanced glycated end-products (AGE), excessively formed in diabetic individuals due to elevated glucose levels, which also activate IKKβ and JNK (reviewed in Solinas and Karin, 2010; Donath and Shoelson, 2011). Apart from adipose tissue, these pathways are activated in multiple tissues and organs in obesity and T2DM and thus represent a promising target for therapeutic intervention.

Moreover, JNK is also activated by insulin but mediates feedback inhibition of insulin signaling and thereby contributes to insulin resistance (Lee et al., 2003b). Interestingly, the insulin/IGF-1 signaling plays also a role for development of cancer and T2DM (reviewed in Melnik et al., 2011). Sugar-rich food in western diet promotes the production of insulin. The resulting insulin/IGF-1 signaling (IIS) activates the phosphatidylinositol 3-kinase (PI3K) and the Akt kinase which mediates the inhibition of transcription factors of the Forkhead box O (FoxO; Cheng and White, 2011) which are supposed to prevent uncontrolled inflammatory response (reviewed in Salih and Brunet, 2008) and represent a link between Western diet and the development of civilization diseases like cancers and T2DM (Melnik et al., 2011; Guevara-Aguirre et al., 2011).

2. Phytochemicals and their effect on inflammation

Natural extracts from plants represent the oldest form of pharmaceutical treatment. A multiplicity of plant extracts with anti-inflammatory properties has been shown to have a significant effect on adipose tissue, to act as anti-diabetic agents, or to be effective for the treatment of chronic inflammatory conditions. Some of these phytochemicals which are abundant in fruits and vegetables and in products thereof like spices, teas, cocoa, or red wine, have been used and consumed for centuries and are known today to act as anti-oxidant and anti-inflammatory agents or to protect from vascular disease or cancer.

2.1. Curcumin

Curcumin is a natural compound extracted from the root of Curcuma longa and is the main component of the Indian curry spice. Curcumin has been used in the traditional Asian medicine for centuries because of its anti-inflammatory properties. It is well known now that curcumin has also anti-oxidant and anti-carcinogenic effects (Park et al., 1998; Duvoix et al., 2005; Shishodia et al., 2005). Its anticancer activity is mainly attributable to the inactivation of HIF-1, as curcumin is known to down-regulate HIF-1α (Bae et al., 2006) and HIF-1β (Choi et al., 2006) and therefore inhibits downstream actions, e.g. angiogenesis, mediated by HIF-1. In addition, curcumin is able to selectively kill tumor cells or to prevent tumorigenesis by interfering with many cellular pathways (Duvoix et al., 2005; Ravindran et al., 2009). It represses NF-κB, inhibits adipogenic transcription factors and the cell cycle, and induces apoptosis (Montopoli et al., 2009; Jutooru et al., 2010; Kim et al., 2011b). In patients with colorectal cancer curcumin treatment upregulates p53 expression (He et al., 2011). For human keratinocytes it was reported that curcumin inhibits TNF-α-induced expression of IL-1β, IL-6 and TNF-α. It enhances the secretion of adiponectin (Ohara et al., 2009) and inhibits insulin-regulated GLUT4 translocation and glucose transport (Ikonomov et al., 2002; Ohara et al., 2009). Ahn et al. (2010) could demonstrate that 10–25 μM curcumin efficiently inhibited differentiation of mouse adipocytes and induced the Wnt signaling pathway. At similar concentrations (10–50 μM) curcumin is able to activate AMPK similar to AICAR (Lee et al., 2009b) and to inhibit the activation of MAPK pathways JNK, p38 MAPK, and ERK in adipocytes (Cho et al., 2007; Ahn et al., 2010). Thus it stimulates proliferation (Kim et al., 2011c) but suppresses lipid accumulation and adipogenesis (Lee et al., 2009b; Ahn et al., 2010; Zhao et al., 2011; Kim et al., 2011b). However, conflicting data exist, how curcumin affects PPARγ ranging from direct activation to inhibition via AMPK (Jacob et al., 2007; Narala et al., 2009; Lee et al., 2009b; Dong et al., 2011; Kim et al., 2011b). Interestingly, curcumin applied at a half maximal inhibitory concentration (IC_{50}) of 45 μM also interferes with cellular energy balance by inhibiting ATP synthesis at the mitochondrial membrane (Zheng and Ramirez, 2000).

In addition, it was demonstrated that active spice-derived components such as curcumin suppress obesity-induced inflammatory responses in adipose tissue from obese mice. As a result, migration and release of MCP-1 and TNF-α were inhibited as well as the release of MCP-1 from adipocytes (Woo et al., 2007). Beyond its anti-inflammatory properties, curcumin also ameliorated diabetes in different mouse models: feeding with 200 mg curcumin/kg diet, which equals the daily intake of 40 mg curcumin for a mouse with a body weight (bw) of 20 mg consuming 4 g diet/day, improved insulin resistance and hyperglycemia. It also elevated the insulin level and lowered the free fatty acid, triglyceride, cholesterol and glucose level in blood and reduced lipid oxidation (Seo et al., 2008). In addition curcumin has been demonstrated to reduce macrophage infiltration into the white adipose tissue, to induce the expression of adiponectin, and to decrease NF-κB activity (Nishiyama et al., 2005; Weisberg et al., 2008). If administered to 500 mg/kg diet, curcumin is able to reduce body weight gain, adiposity and the expression of VEGF in mice (Ejaz et al., 2009). Similar positive, anti-hyperlipidemic and anti-diabetic effects were also seen in rats (Asai and Miyazawa, 2001; Pari and Murugan, 2007) and hamsters (Jang et al., 2008).

Taken together, these data indicate that curcumin is able to repress inflammation and obesity, thereby improving the chronic condition in diabetes. However, the efficacy of phytochemicals under physiological conditions is, in general, largely limited by their low solubility and therefore their poor bioavailability. This is especially true for curcumin, with only its conjugates, glucuronides or sulfates, being generally detectable in plasma, whereas unconjugated curcumin being below 0.1 μg/ml, (0.27 μM respectively), even after consumed dosages as high as 12 g/day (Vareed et al., 2008; Dhillon et al., 2008; Kanai et al., 2011). These conjugates rapidly appear in plasma with a time of peak concentration (T_{max}) and half-life ($T_{1/2}$) of about 3.3 h and 6.8 h (Vareed et al., 2008). Thus nanoparticle formulation has recently been demonstrated to improve its plasma levels and bioavailability (Sasaki et al., 2011; Kanai et al., 2012) and a modification by linking polyethylene glycol is able to enhance the delivery into adipocytes (Kim et al., 2011a). Complexed with phosphatidylcholine, curcumin has been proven to significantly improve the inflammatory status (Belcaro et al., 2010). Despite its very limited absorption and bioavailability, even unmodified curcumin ameliorates the antioxidative status and cholesterol level and ameliorates T2DM associated parameters, if administered to human, as demonstrated in recent studies (Table 1). Given the curcumin concentrations applied in vitro, most likely curcumin metabolites rather than the parent compound may largely contribute to curcumin's biological activity (Pfeiffer et al., 2007; Somparn et al., 2007).

2.2. Capsaicin

Capsaicin is the active component in chili peppers and is widely used as a spice but also for topical treatment of cutaneous allergy and neurological disorders such as diabetic neuropathy. It is produced by the plant to discourage unsuitable frugivores and to protect against fungal infection (Tewksbury and Nabhan, 2001; Tewksbury et al., 2008). Capsaicin specifically binds the vanilloid receptor (VR1), an ion channel which is activated by several physical and chemical stimuli, and thereby causes the pungent sensation in mammals (Caterina et al., 1997).

The structure of capsaicin is similar to that of curcumin and it is also well known to have anti-inflammatory effects (Surh, 2002). Further investigations demonstrated that capsaicin can activate AMPK and inhibit adipocyte differentiation in mouse adipocytes (Hwang et al., 2005). In murine macrophages, capsaicin's anti-inflammatory action was demonstrated by repressed expression of pro-inflammatory gene iNOS. It also represses COX2 activity, thereby inhibits PGE_2 production, and inactivates NF-κB by blocking IκBα degradation (Kim et al., 2003). Additionally, capsaicin binds specifically to PPARγ and inhibits the production of TNF-α. Therefore its anti-inflammatory effect is supposed to be mediated via activation of PPARγ and inactivation of NF-κB (Park et al., 2004; Kang et al., 2007). Screening different plant extracts also determined its potential to activate PPARα (Mueller et al., 2011). In mouse adipocytes, it inhibits adipogenesis and lowers the amount of intracellular triglycerides. Apart from that, it also decreases the mitochondrial membrane potential, activates caspase, decreases anti-apoptotic Bcl-2 and increases pro-apoptotic Bax and Bak protein levels, thereby inducing apoptosis. Most of these effects were apparent even at concentrations below 50 μM (Hsu and Yen, 2007). It is already known that thermogenesis, a feature that was thought to be mediated just by brown but not by white adipocytes, is enhanced by capsaicin (Osaka et al., 1998). By stimulating lipolysis and thermogenesis capsaicin thus increases the energy expenditure in adipose tissue (Diepvens et al., 2007). More recently, a capsaicin-induced concentration-dependent (0.1–10 μM) up-regulation of the mitochondrial uncoupling protein 2

(UCP-2), a mitochondrial proton transporter, which separates oxidative phosphorylation from ATP synthesis with energy dissipated as heat and other genes involved in lipid catabolism has been discovered also in white adipocytes (Lee et al., 2011). A further study with adipocytes demonstrated that the mentioned activation of VR1 by capsaicin concentrations starting from 10 nM promotes a calcium influx and finally prevents adipogenesis and obesity, which has been confirmed in vivo too (Zhang et al., 2007). This property of capsaicin likely explains the activation of further downstream targets.

In earlier studies with rats, capsaicin has been shown to stimulate lipid mobilization from adipose tissue and to lower the perirenal adipose tissue weight and serum triglyceride concentration if supplemented at 0.014% of the diet, which is related to that usually ingested by rural Thai people (Kawada et al., 1986a). This was also associated with an enhanced energy metabolism and an increased respiratory quotient (Kawada et al., 1986b). Further studies in mice suggest that capsaicin suppresses obesity-induced inflammation by modulating adipokine release: dietary capsaicin (0.015% of diet) markedly decreased fasting glucose, insulin, and triglyceride levels. In addition, it suppressed the expression and secretion of IL-6 and MCP-1 from obese adipose tissues but enhanced it for adiponectin. If administered intraperitoneally (2 mg/kg bw) it inhibited macrophage activation for release of pro-inflammatory mediators and stopped their migration (Kang et al., 2007, 2011). Moreover, capsaicin also counteracts the pro-inflammatory effect of saturated fatty acids, as it significantly reduced JNK activation, induced by palmitic acid (Choi et al., 2011). Thus, capsaicin may be regarded as a useful phytochemical for attenuating obesity-induced inflammation and obesity-related pathologies. In previous studies an increased fat oxidation in overweight subjects treated with capsaicin (Lejeune et al., 2003), and a lowered fat intake (Yoshioka et al., 2004) was measured. As summarized in Table 1, more recent studies investigating the effect of dietary capsaicin display also an impact on glucose and insulin. Moreover, capsaicin also seems to be involved in regulation of energy expenditure and in the activation of brown adipose tissue in humans. Pharmacokinetic analysis revealed that after oral intake of 5 g fresh chili containing 26.6 mg capsaicin, capsaicin is rapidly absorbed within 10 min and metabolized with a $T_{1/2}$ of 25 min, the maximal plasma concentration was at 2.5 ng/ml (8 nM; Chaiyasit et al., 2009). With a daily chili intake comparable to that in Korea, which is about 7 g (Ku and Choi, 1990), some effects as reported in vitro might also be accessible by dietary consumption.

2.3. Gingerol

Ginger is the underground stem of the plant *Zingiber officinale* and probably originates from southern china. It is widely used for cooking as a spice and as herbal medicine. Within ginger extracts, gingerols have been identified as the major bioactive components, and 6-gingerol with a concentration of about 1.3–1.9 mg/g ginger is the most abundant component, known to have a strong anti-inflammatory activity (Ojewole, 2006; Jiang et al., 2006). Gingerols also possess immunosuppressive (Lu et al., 2011) and anti-tumor-promoting properties: They inhibit the expression of COX-2 by blocking p38 MAPK and NF-κB activation (Kim et al., 2005) and have also been shown to suppress TNF-α expression and to inhibit inflammation and tumor promotion after application to the skin of mice (Park et al., 1998; Surh et al., 1999). However, it has been shown recently that 6-gingerol can up-regulate HIF-1α during mouse embryogenesis to prevent developmental disorders in the context of hypoxia (Yon et al., 2011). In addition, ginger extracts down-regulate telomerase activity and c-myc in human lung carcinoma cells (Tuntiwechapikul et al., 2010). Although PPARγ is not affected by gingerol, which is in contrast to other phytochemicals (Isa et al., 2008), treatment of mouse adipocytes with gingerol enhances differentiation and increased insulin-sensitive and glucose uptake; hence it is expected to improve the diabetic state too (Sekiya et al., 2004). Furthermore, 6-gingerol at concentrations of 10 and 25 μM was shown to have further impact on the regulation of adipocyte function by inhibiting TNF-α-mediated inhibition of adiponectin expression in mouse adipocytes via inhibiting JNK phosphorylation (Isa et al., 2008).

Due to its structural homology to spice-derived compound capsaicin, gingerol is a further VR1 agonist (Dedov et al., 2002) which might play a role for suppressing inflammatory responses of adipose tissue in obesity (Woo et al., 2007). 6-Gingerol injected intraperitoneally at 25 mg/kg bw significantly decreased the metabolic rate in rats (Ueki et al., 2008), supporting a mitochondrial disruption (Eldershaw et al., 1992). In a streptozotocin-induced diabetic rat model, animals fed a high fat diet displayed a significantly elevated serum insulin concentration and better glucose tolerance if their diet was enriched with 2% ginger (Islam and Choi, 2008). In a similar model, the daily intraperitoneally administration of raw ginger extract (500 mg/kg bw) significantly lowered serum glucose, cholesterol and triacylglycerol levels and reversed diabetic proteinuria (Al Amin et al., 2006). A recent in vivo study using high-fat fed mice attested a significantly reduced body weight gain and adiposity in association with a modified cholesterol metabolism and fatty acid oxidation after 0.05% 6-gingerol supplementation of their diet (Beattie et al., 2011). However, to get an equivalent content of 6-gingerol, a daily consumption of about 2.5 g of fresh ginger rhizome per kg bw (referred to a 30 g mouse consuming 3 g/day) would be necessary. Moreover, the administration of a ginger extract to diabetic rats (200 mg/kg bw) lowered their blood glucose levels and affected intra and extra-mitochondrial enzyme activities (Ramudu et al., 2011). These animal studies indicate that ginger possesses hypoglycaemic, hypocholesterolemic and hypolipidemic potential and therefore may be of value in human subjects.

There are only few recent clinical trials focussing the applicability of gingerol for treatment of diabetes or related purposes in man. Data obtained in recent studies administering doses between 100 mg and 3 g indicate that gingerol is able to lower lipid and eicosanoid levels (Table 1). 6-Gingerol, the main component of ginger extracts, is readily absorbed after oral consumption and metabolized to glucuronide and sulfate conjugates, as demonstrated in pharmacokinetic studies. The $T_{1/2}$ of gingerol and its metabolites range from 1 to 3 h in human plasma and no accumulation is observed in plasma and colon tissues after multiple daily dosing due to rapid clearance (Yu et al., 2011). However the intake of 2 g ginger extract has been demonstrated to be unable to lead to detectable amounts of free 6-gingerol in plasma (Zick et al., 2008; Yu et al., 2011). Gingerol conjugates may be more biologically active than the parent compound, warranting their further investigation.

2.4. Catechin

Catechins are flavanols, comprising catechin (C), epicatechin (EC), gallocatechin (GC), epigallocatechin (EGC), and their gallates. About 70 years ago, a surprisingly low blood pressure was discovered among the Kuna Indians, a population living on an archipelago out of the Caribbean coast of Panama (Kean, 1944). Although they are not genetically protected, it has been discovered that they live longer than other Panamanians, and have a reduced frequency of diabetes mellitus, myocardial infarction, stroke, and cancer. Interestingly, it has been reported that for the Indians, their main drink is cocoa, a beverage made of the cocoa (or cacao) bean. Per individual Kuna, there was an average intake of 35 cups cocoa per week and for some it was the only source of drinking water.

Cocoa is very rich in catechins and the flavanol-based oligomers known as procyanidins (Hollenberg, 2006). Procyanidins have a beneficial effect on inflammatory diseases such obesity and type 2 diabetes as they can modulate inflammation, by reducing e.g. the expression of IL-6 and MCP-1 and enhancing the production of the anti-inflammatory adipokine adiponectin (Chacon et al., 2009). Apart from cocoa, high

Table 1
Overview of recent clinical trials testing phytochemicals with respect to diabetic and inflammatory markers.

Treatment group	Dose; duration	Ref.	Effect
Curcumin			
25 T2DM patients	200 mg curcumin (1000 mg Meriva)/d; 4 w	Appendino et al. (2011)	Significant improvement of diabetic microangiopathy
10/9 healthy	500 mg/6000 mg curcumin/d; 7 d	Pungcharoenkul and Thongnopnua (2011)	Significant decrease of serum cholesterol and triglyceride levels (more pronounced at the lower dose than at the higher one); increase of antioxidant capacity
20 T2DM nephropahty patients	66.3 mg curcumin (1500 mg tumeric)/d; 2 m	Khajehdehi et al. (2011)	Attenuated proteinuria, TGF-β and IL-8 levels
50 patients with osteoarthritis	200 mg curcumin (1000 mg Meriva)/d; 8 m	Belcaro et al. (2010)	Significant reduction of inflammatory markers (IL-1β, IL-6, sCD40L, sVCAM-1, ESR)
21 patients with β-thalassemia/Hb E	500 mg curcuminoids (357 mg curcumin, 107 mg demethoxycurcumin, and 36 mg bisdemethoxycurcumin)/d; 12 m	Kalpravidh et al. (2010)	Improvement of oxidative stress level
15/14/15 patients with ACS	45/90/180 mg curcumin (2/4/8 g curcuma extract)/d; 2 m	Alwi et al. (2008)	Trend of reduction in total cholesterol and LDL cholesterol level by low-dose curcumin administration
8/11 healthy	1/4 g curcumin/d; 6 m	Baum et al. (2007)	No significant effect on serum cholesterol or triacylglycerol concentrations
Capsaicin			
18 healthy male	9 mg capsinoids; once (FDG-PET)	Yoneshiro et al. (2012)	Activation of brown adipose tissue, increase of energy expenditure
25 healthy	1 g red pepper (1995 μg capsaicin, 247 μg nordihydrocapsaicin, and 1350 μg dihydrocapsaicin); once	Ludy and Mattes (2011)	Increased energy expenditure and body temperature
12 healthy	26.6 mg capsaicin (5 g capsicum); once (OGTT)	Chaiyasit et al. (2009)	Significantly lowered plasma glucose levels; significant higher insulin levels
27 healthy	510 mg cayenne/510 mg cayenne t.w. green tea; once	Reinbach et al. (2009)	Reduction of energy intake and hunger and increased satiety (in combination with green tea)
36 healthy	33 mg capsaicin (30 g chili blend [55% cayenne chili])/d; 4 weeks	Ahuja et al. (2007)	No change of metabolic parameters (plasma glucose, serum lipids, lipoproteins, insulin, metabolic rate)
14 helthy	400 μg capsaicin; once (glucose loading test)	Dömötör et al. (2006)	Slight increase of glucose absorption and glucagon release
27 healthy	33 mg capsaicin (30 g chili blend [55% cayenne chili])/d; 4 weeks	Ahuja and Ball (2006)	Inhibited oxidation of serum lipoproteins; no difference in the serum lipid, lipoproteins, total anti-oxidation status
36 healthy	33 mg capsaicin (30 g chili blend [55% cayenne chili])/d; 4 weeks	Ahuja et al. (2006)	Attenuated postprandial hyperinsulinemia
Gingerol			
16 healthy	2 g ginger extract/d; 28 d	Zick et al. (2011)	Significant decrease in PGE_2 and other eicosanoids
45 patients with hyperlipidemia	3 g ginger/d; 45 d	Alizadeh-Navaei et al. (2008)	Significant reduce in triglyceride, cholesterol, LDL, VLDL
35/35 healthy	300/600 mg NT (t.w. GA)/d; 24 w	Roberts et al. (2007)	ineffective in causing weight loss or in suppressing food intake
Catechin			
15 ow-ob	650 ml green tea (534 mg catechins t.w. 11.7 g inulin)/d; 6 w	Yang et al. (2012)	Significant reduction of body weight, fat mass, body mass index, and blood pressure
64 ow-ob male	1060 mg GTE (424–753 mg EGCG t.w. 170–286 mg EGC, 85–784 mg EC)/d; 6 w	Brown et al. (2011)	Decreased body weight; no effect on blood pressure or biomarkers of metabolic function
80 T2DM patients	1500 mg GTE (856 mg EGCG)/d; 16 w	Hsu et al. (2011)	No significant difference in fasting glucose, HbA1C, hormone peptides, and plasma lipoproteins
19 healthy males	491 mg catechins t.w.oolong tea/d; 5 d	Baer et al. (2011)	No effect on glucose metabolism
8 healthy	405 mg EGCG/d; 2 d	Lonac et al. (2011)	No influence on resting metabolism and the thermic effect of feeding
13/10 ob patients with MetS	4 cups green tea (440 mg EGCG t.w 220 mg EGC, 180 mg ECG, and 88 mg EC)/2 capsules GTE (460 mg EGCG t.w. 240 mg EGC, 120 ECG, and 50 mg EC)/d; 8 w	Basu et al. (2011) and Basu et al. (2010)	Significant decrease of body weight, BMI, lipid peroxidation, and plasma serum amyloid alpha; no effect on inflammatory markers or features of MetS
47/49/43 ow	458 mg green tea catechins t.w. 104 mg caffeine/468 mg catechin t.w. 126 mg caffeine/886 mg catechins t.w.198 mg caffeine/d; 90 d	Wang et al. (2010)	Significantly decreased intra-abdominal fat, waist circumference and body weight with highest dose; significantly reduced total body fat mass with low and medium doses; no effect on plasma HDL cholesterol and LDL cholesterol levels, plasma triglycerides, and glucose
10 ow-ob male	300/600 mg EGCG/d; 3 d	Thielecke et al. (2010)	No effect on energy expenditure; increase of postprandial fat oxidation only by low EGCG dose
10 helathy smokers	580 mg green tea catechins (102 mg EGCG, 77 mg EGC, 30 mg ECG, 129 mg GCG, 138 GC, 38 mg C)/d; 2 w	Oyama et al. (2010)	Increase of NO production and decrease of oxidative stress; decrease of MCP-1 level
100 pulmonary tuberculosis patients	500 μg (!) catechin extract 3×/week; 4 m	Agarwal et al. (2010)	Reduce of oxidative stress with significantly decreased lipid oxidation and increased NO levels
46 ow-ob male	800 mg EGCG;/d; 8 w	Brown et al. (2009)	No effect on insulin sensitivity, insulin secretion or glucose tolerance; reduction of diastolic blood pressure
23 T2DM patients	583 mg green tea catechins/d; 12 w	Nagao et al. (2009)	Significant decrease in waist circumference; significantly increased adiponectin and insulin levels; no effect on glucose and hA1c

Table 1 (*continued*)

Treatment group	Dose; duration	Ref.	Effect
21 ob children	576 mg green tea catechins/d; 24 w	Matsuyama et al. (2008)	Significant decrease in waist circumference, systolic blood pressure, and LDL cholesterol
12/11 healthy male	3 capsules GTE (366 mg EGCG)/d; 1 d	Venables et al. (2008)	Increased fat oxidation during exercise; improved insulin sensitivity and glucose tolerance
60 with elevated blood glucose	GTE powder (456 mg catechins t.w. 102 mg caffein)/d; 2 m	Fukino et al. (2008)	Significant reduction in HbA1c and diastolic blood pressure; no effect on weight, body fat, systolic blood pressure, HOMA index, serum lipid and glucose level
29 healthy	500 mg green tea catechins/d; 4 w	Inami et al. (2007)	Significant decrease of oxidized LDL cholesterol
16/17 T2DM patients	150/300 mg green tea catechins t.w. 75 mg of black tea theaflavins/d; 3 m	Mackenzie et al. (2007)	No effect on HbA1c
19 ow-ob, pmp women	300 mg EGCG/d; 12 w	Hill et al. (2007)	Reduction of heart rate and plasma glucose concentration in subjects with impaired glucose tolerance
6 ow males	300 mg EGCG/d; 2d	Boschmann and Thielecke (2007)	Significantly lower respiratory quotient; no effect on energy expenditure
Resveratrol			
11 ob	150 mg resveratrol/d; 30 d	Timmers et al. (2011)	Reduced metabolic rate, mimicking effect of calorie restriction
10 T2DM patients	10 mg resveratrol/d; 4 w	Brasnyo et al. (2011)	Significantly decrease of insulin resistance
10/10/10/10 healthy	0.5/1/1.5/2 g resveratrol/d; 29 d	Brown et al. (2010)	Reduction of IGF-I and IGFBP-3 in plasma but gastrointestinal symptoms on 2 highest dose levels
10 healthy	200 mg PCE (40 mg resveratrol)/d; 6 w	Ghanim et al. (2010)	Suppressive effect on oxidative and inflammatory stress
Genistein			
23 patients with prostate cancer	30 mg genistein/d; 3–6 w	Lazarevic et al. (2011)	Significantly lowered blood cholesterol
43 healthy, ob, pmp women	60.8 mg genistein (t.w. 16 mg daidzein + 3.2 mg glycitein)/d; 6 m	Llaneza et al. (2011)	Significant increase of adiponectin serum levels
71 pmp osteopenic women	54 mg genistein/d; 24/36 m	Marini et al. (2010)	Significantly decreased fasting glucose and insulin, HOMA-IR, fibrinogen and homocysteine after 24/36 months of treatment
30 pmp normo- and hyperinsulinemic women	54 mg genistein/d; 24 w	Villa et al. (2009)	Decreased fasting glucose in normoinsulinemic patients; significant reduction in fasting insulin, fasting C-peptide; significantly improved HDL cholesterol levels in hyperinsulinemic patients
32 healthy, pmp women	64 mg genistein (t.w. 63 mg daidzein and 34 mg glycitein)/d; 12 w	Charles et al. (2009)	Significant increase in serum adiponectin levels; no effect on metabolic parameters
25 pmp women	2 mg genistein (t.w. 4.8 mg daidzein)/d; 6 m	Rios et al. (2008)	No significant effect
Quercetin			
20 athletes	1000 mg quercetin t.w. 1000 mg Vitamin C, 40 mg niacinamide 120 etc.; once	Konrad et al. (2011)	No postexercise inflammation or immune changes
334/333	500/1000 mg quercetin (t.w. 125/250 mg Vit. C and 5/10 mg niacin)/d; 12 w	Knab et al. (2011)	Little decrease in HDL cholesterol level and IL-6
12 sarcoidosis patients	2000 mg quercetin within 24 h	Boots et al. (2011)	Reduced oxidative stress and inflammation markers in blood
6 healthy women	150 mg quercetin; once	Egert et al. (2011)	No changes for respiratory quotient, resting energy expenditure, pulse or blood pressure
38/40 healthy women	500/1000 mg quercetin/d; 12 w	Heinz et al. (2010)	No influence on innate immune function or inflammatory markers IL-6 and TNF-α or body fat
93 ow patients with MetS	150 mg quercetin/d; 6 w	Egert et al. (2010)	Lowered blood pressure and reduction in HDL cholesterol, significant decrease of plasma oxidized LDL and TNF-α (dependent on apolipoprotein E genotype)
20 patients with rheumatoid arthritis	498 mg quercetin (t.w. 399 mg Vit. C)/d; 4 w	Bae et al. (2009)	No significant change of inflammation markers in blood
93 ow with MetS	150 mg quercetin/d; 6 w	Egert et al. (2009)	Decreased blood pressure, serum HDL-cholesterol and significantly declined oxidized LDL plasma concentration; no effect on TNF-α
35 healthy	50–150 mg quercetin/d; 2 w	Egert et al. (2008)	No effect on oxidized LDL- and TNF-α concentration; no significant change of serum lipids, lipoproteins, body composition, and resting energy expenditure

ACS: acute coronary syndrome; MetS: metabolic syndrome; ow = overweight; ob = obese; pmp = post menopausal; d: days; w: weeks; m: months; ESR: erythrocyte sedimentation rate HbA1c: hemoglobin A_{1c}; HOMA: homeostatic model assessment; FDG-PET: [^{18}F]fluorodeoxyglucose–positron emission tomography; OGTT: oral glucose tolerance test; GTE: green tea extract; EGCG: epigallocatechin gallate; EGC: epigallocatechin; ECG: epicatechin gallate; EC: epicatechin; C: catechin; GC: gallocatechin; GCG: gallocatechin gallate; GA: gallic acid; t.w.: together with.
NT: 40% rhubarb 13.3% astragulus, 13.3%, red sage, 26–27% turmeric, and 6–7% ginger; GA: gallic acid; PCE: *Polygonum cuspidatum* extract; numbers in the treatment group refer to study subjects receiving phytochemicals, not control/placebo (except for cross over studies); phytochemicals were either administered once or over a specified period as indicated.

quantities of catechins and their oligomers can also be found in green tea, grapes and red wine. They are known to act pro-apoptotic and anti-cancerogenic, although not all members of the catechins share common action patterns (Leone et al., 2003).

Epigallocatechin gallate (EGCG), the most bioactive catechin in green tea, is an anti-inflammatory compound, too. It has been known for a while to interfere with MAPK pathways (Chung et al., 2001) and to be able to block NF-κB activation by inhibiting IκBα

degradation (Muraoka et al., 2002). The inhibition of this key transcription factor is responsible for the down modulation of iNOS transcription and NO production in macrophages (Lin and Lin, 1997) and in chondrocytes (Singh et al., 2002). In contrast, regarding vascular inflammation, EGCG provides its anti-inflammatory activity by enhancing NO production to block endothelial exocytosis and leukocyte adherence to endothelial cells (Yamakuchi et al., 2008). This anti-inflammatory effect is mediated by increased phosphorylation level of eNOS and Akt. Similarly, catechin and epicatechin are also known to increase NO levels in endothelial cells (Steffen et al., 2007; Ramirez-Sanchez et al., 2010; Brossette et al., 2011).

In addition, EGCG blocks NF-κB activation in human endothelial cells and thereby inhibits MCP-1 expression (Hong et al., 2007). Apart from that, EGCG as well as other catechins with a gallocatechin moiety or a galloyl residue acts as AMPK activators (Murase et al., 2009). Catechins have also been demonstrated to differentially regulate HIF-1α expression and activation (Zhou et al., 2004; Thomas and Kim, 2005; Zhang et al., 2006; Lin et al., 2008; Domingo et al., 2010) and to activate PPARβ/δ, thus also reducing NO production in cardiomyocytes (Danesi et al., 2009). Moreover, they counteract apoptosis by reducing caspase3 activity and decreasing the expression of caspase3 and bax mRNA (Park et al., 2006; Hara et al., 2006; Yu et al., 2007).

Of note, EGCG specifically inhibits the proteasome in vitro (IC_{50} = 86–194 nM) and in vivo (1–10 μM) (Nam et al., 2001), and this feature has major consequences for cellular signaling and may be causative for its anti-inflammatory properties. In adipocytes, EGCG at concentrations of 5–10 μM clearly promotes expression of genes which are involved in insulin sensitivity (Sakurai et al., 2009), and in uncoupling mitochondrial ATP synthesis from respiration, thereby influencing thermogenesis and energy expenditure (Lee and Kim, 2009). Interestingly, catechins also stimulate thermogenesis in brown adipose tissue (Dulloo et al., 2000). It has been recently elucidated that EGCG activates the PI3K/AKT pathway and inactivates the MEK/ERK pathway, which results in an inactivation of FoxO1 and thereby inhibits differentiation from preadipocytes to mature adipocyte (Nakae et al., 2003; Kim and Sakamoto, 2011). At the same time, procyanidins have been shown to inhibit LOX-1, a receptor for oxidized LDL in several cells, including endothelial cells and macrophages, and that this might be, at least partially, the underlying mechanism of the well-known vascular protective effects of red wine described in the French Paradox (Nishizuka et al., 2011). Of note, a recent study with Austrian red wines exhibited for 100 ml of the tested wines an effect for PPARγ activation which was equivalent to approximately four times the daily dose of rosiglitazone (Zoechling et al., 2011). Furthermore, C and EC were recently detected in the extract from the traditional medical plant *Sarcopoterium spinosum*, which was demonstrated to have an anti-diabetic effect in a mice and mimicked the action of insulin (Smirin et al., 2010).

In rats, catechins significantly lower oxidative stress and pro-inflammatory cytokine levels, increase catalase and superoxide dismutase and decrease iNOS, TNF-α, and NF-κB expression (Suzuki et al., 2007; Abd El-Aziz et al., 2011). Furthermore, daily feeding a high-fat diet supplemented with EGCG (1 mg/kg bw) for 16 weeks elevated thermogenesis, improved glucose tolerance and increased expression of PPARγ (Chen et al., 2009b). In streptozotocin-diabetic rats, a daily administration of 25 mg/kg bw for 8 weeks produced a hypoglycemic effect, ameliorated the lipid profile and attenuated lipid peroxidation (Roghani and Baluchnejadmojarad, 2009, 2010). A recent in vivo study with diabetic mice given an epicatechin-enriched diet displayed significantly reduced IGF-1 levels and, consistently, also a prolonged lifespan; similar results were seen in Drosophila. Hence epicatechin has been considered a novel food-derived, anti-aging compound (Si et al., 2011).

In some human studies, the ingestion of catechins could ameliorate diastolic blood pressure, LDL cholesterol, obesity and also cardiovascular disease risk factors. In patients with T2DM, a catechin-rich beverage was able to improve obesity and blood glucose control, although no significant effect was seen in other trials (Table 1). Conflicting results between these studies may be in part related to different food consumed by the participants during the intervention of course affecting major outcome variables, or by divergent production methods, application forms and doses themselves. Moreover, the stereochemical configuration of catechins is also known to influence metabolism and biological activity (Ottaviani et al., 2011). A recent pharmacokinetic analysis revealed maximum plasma concentrations of 1.09, 0.41, 0.33, and 0.16 μM for EGCG, EGC, EC, and ECG after ingestion of 836 mg green tea catechins (composed of 448, 178, 96, and 66 mg of the respective catechin) (Miller et al., 2012). With respect to data in Table 1, the daily consumption of 6–8 cups of a moderate-strength green tea, which approximately equals the intake of 800 mg catechins (Khokhar and Magnusdottir, 2002), seems to be beneficial for counteracting oxidative stress and inflammatory triggers as well as obesity. This is also in good accordance with a previous meta-analysis suggesting that a consumption of four or more cups tea per day may lower the risk for developing T2DM (Jing et al., 2009).

2.5. Resveratrol

Resveratrol is a non-flavonoid polyphenol produced naturally by numerous plants including grapes, peanuts, cranberries, blueberries and Japanese knotweed. In fresh grape skin the resveratrol content ranges from 50 to 100 μg/g and from 0.1 to 14 mg/l in red wine (Pervaiz, 2003; Mark et al., 2005). It is synthesized in plants in response to injury or fungal attack. Its supposed health benefits and the relatively high abundance in some red wine have initiated a vigorous examination of its action. Thus it has been demonstrated that plasma concentrations of resveratrol produced by moderate wine intake significantly increased blood platelet NO production and inhibited p38MAPK phosphorylation (Gresele et al., 2008). Different studies indicate that resveratrol has an anti-inflammatory effect and acts as an anti-oxidant agent: it ameliorates inflammation by counteracting TNF-α-induced effects and attenuates mRNA expression and secretion of different adipokines like PAI-1, IL-1β, IL-6, IL-8 and MCP-1. On the other hand, it stimulates expression and multimerization of adiponectin and down-modulates JNK in different adipocyte models (Ahn et al., 2007; Zhu et al., 2008; Chuang et al., 2010; Olholm et al., 2010; Wang et al., 2011). These effects of resveratrol are probably all mediated through or associated with the down-regulation of the NF-κB pathway (Tsai et al., 1999; Holmes-McNary and Baldwin, 2000; Ahn et al., 2007).

Furthermore, it inhibits prostaglandin E2 production in macrophages from mice (Martinez and Moreno, 2000) and rats (Leiro et al., 2004) and represses production of iNOS-2 and COX-2 and, consequently, also of reactive oxygen and nitrogen species (Tsai et al., 1999; Martinez and Moreno, 2000; Chan et al., 2000; Leiro et al., 2002, 2004; Gresele et al., 2008). Since oxidative stress is associated with neurodegenerative diseases, resveratrol was also demonstrated to feature neuro-protective properties (Morin et al., 2003; Choi et al., 2007; Yanez et al., 2011). Resveratrol also counteracts adipogenesis (Hwang et al., 2010; Vigilanza et al., 2011; Chen et al., 2011), is able to induce a cell cycle arrest (Kim et al., 2004; Panayiotidis et al., 2006; Lee et al., 2009a) and has a pro-apoptotic effect in adipocytes of mice and human (Rayalam et al., 2008; Mader et al., 2010). Of note some of resveratrol's features also may account for brown adipocytes, which has been demonstrated in the case of apoptosis induction (Miranda et al., 2010).

Resveratrol has been described to down-regulate PPARγ expression, thereby decreasing GLUT4 expression. However, inconsistent data have been described for glucose uptake (Floyd et al., 2008; Fischer-Posovszky et al., 2010). Interestingly, resveratrol also counteracts insulin resistance, delipidation, and inflammation in human

adipocytes mediated by conjugated linoleic acid (Kennedy et al., 2009).

Resveratrol is a potent suppressor of HIF-1α by inhibiting MAPK activation and insulin/IGF-1 signaling and induces HIF-1α degradation via the proteasomal pathway (Cao et al., 2004; Zhang et al., 2005). It suppresses HIF-1 expression in the context of hypoxia (Park et al., 2007; Wu et al., 2008) and is able to protect myocardial cells from hypoxia-induced cell death by regulating expression and activity of FoxO1 via the deacetylase sirtuine 1 (Sirt1; Chen et al., 2009a). Sirt1 is involved in fat metabolism and adipogenesis; its activation promotes lipolysis and loss of fat, by repressing PPARγ (Picard et al., 2004) and in the end leads to increased longevity (Guarente, 2006). Following the first description that Sirt1 is activated by resveratrol (Howitz et al., 2003), many studies supported this observation, although there are conflicting data as well (Kaeberlein et al., 2005; Borra et al., 2005; Zhang, 2006; Backesjo et al., 2006; de Boer et al., 2006; Pedersen et al., 2008; Beher et al., 2009; Alcain and Villalba, 2009; Chen et al., 2009a; Pacholec et al., 2010; Fischer-Posovszky et al., 2010; Zhu et al., 2011) and the ability of resveratrol to activate Sirt1 is still in doubt (Stünkel and Campbell, 2011). Likewise, the effect of resveratrol on FoxO1 expression is disputed (Subauste and Burant, 2007; Bai et al., 2008; Costa et al., 2011). Resveratrol affects the metabolic activity in adipocytes and thus is known to mimic the effect of caloric restriction. It counteracts the antilipolytic action of insulin and inhibits the de novo lipogenesis by down-regulation of lipogenic gene expression at concentrations higher than 10 μM (Floyd et al., 2008; Szkudelska et al., 2009; Shan et al., 2009; Fischer-Posovszky et al., 2010). Moreover, Szkudelska et al. (2011) could demonstrate that resveratrol applied at similar dose range (6–50 μM) substantially reduced ATP levels in adipocytes, most likely by interfering with the respiratory chain at the inner mitochondrial membrane. As the inhibition of ATP synthase and complex III of the electron transport chain have been reported previously (Zini et al., 1999; Zheng and Ramirez, 2000; Kipp and Ramirez, 2001), a depletion of ATP may also be responsible for further AMPK-mediated changes in metabolic pathways.

In their study, Baur and colleagues reported, that the physiology of mice consuming excess calories was shifted to that on a standard diet by a daily resveratrol administration to the diet of 22 mg/kg bw for 6 months, thereby significantly increasing their survival. This longer lifespan was associated with increased insulin sensitivity, reduced IGF-I levels, and activation of AMPK (Baur et al., 2006). In addition, feeding resveratrol at 400 mg/kg bw/day protects obese mice against obesity and insulin resistance (Lagouge et al., 2006). In rats, even smaller doses between 0.5 and 60 mg/kg bw/day reduce body fat, dyslipidemia, hyperleptinemia, hypertension and stimulate glucose uptake, similar to insulin but through a different mechanism (Su et al., 2006; Rivera et al., 2009; Macarulla et al., 2009). More recently, a reduction in body mass gain was also observed in the non-human primate species, gray mouse lemur, after administration of less than 200 mg resveratrol/kg bw/day (Dal Pan et al., 2010).

Comparable metabolic effects were also seen in humans: in healthy obese men, a resveratrol supplementation lowered oxidative stress and mimicked the effect of calorie restriction, and in T2DM patients, it significantly improved insulin sensitivity (Table 1). Of interest, these effects were achieved with doses far beneath those from mice studies. Timmers et al. (2011) obtained average plasma resveratrol levels of 231 ng/ml in human after treatment with 150 mg/day for 30 days, which were even higher than those measured in mice (10–120 ng/ml) by Lagouge et al. (2006), suggesting different metabolic rates between human and mouse. After ingestion, resveratrol is rapidly absorbed and metabolized in human with a $T_{1/2}$ of 5–10 h and resveratrol-3-O-sulfate as the most abundant circulating metabolite (Brown et al., 2010). Clinically applied daily doses range from 10 mg to 5 g, whereas those beyond 2.5 g cause gastrointestinal events. Noteworthy, such doses generated average and maximal plasma concentrations of 126 ng/ml (0.55 μmol/l) and 967 ng/ml (4.24 μmol/l) respectively (Brown et al., 2010), and this is not dramatically below levels at which resveratrol elicits biochemical effects in vitro (10 μmol/l), as mentioned above. However, in contrast to the catechin content in green tea, resveratrol content in standard diet is far from being sufficient to attain those concentrations in vivo.

2.6. Genistein

The isoflavone genistein is a naturally occurring phytoestrogen, which is particularly high concentrated in soy and soy-derived products. In Japan, the approximate daily intake of isoflavones is 25–50 mg and reaches even up to 100 mg in 10% of Asian population (Messina et al., 2006), in contrast to 0.15–3 mg in the U.S. (Horn-Ross et al., 2001; de Kleijn et al., 2001). It has been known for a while to be a potent inhibitor of protein tyrosine kinase (Akiyama et al., 1987) and eukaryotic DNA topoisomerase II (Okura et al., 1988; Markovits et al., 1989). Similarly to other topoisomerase inhibitors, genistein is able to induce apoptosis (McCabe and Orrenius, 1993). Genistein is a potent inhibitor of angiogenesis and has a broad inhibiting effect on proliferating cells (Fotsis et al., 1995). Its possible suitability as a pharmacological agent has been investigated, since it has been demonstrated that people in Asia consuming large amounts of genistein-rich soy products are more seldom affected by breast or prostate cancer (Muir et al., 1987; Severson et al., 1989) and by T2DM (Odegaard et al., 2011).

In hypoxic conditions, genistein has been demonstrated to inhibit the HIF1α expression and accumulation and the activation of ERK (Wang et al., 2005; Li et al., 2008). Moreover, genistein appears to provide a protective effect on myocardial and endothelial cells, as it triggers the exocytosis of the cardioprotective neuropeptide calcitonin gene-related peptide. This is a result of VR1-mediated action, of which genistein is supposed to be a direct activator, too (Li et al., 2009), apart from capsaicin and gingerol.

In adipocytes, genistein acts anti-inflammatory and down-modulates leptin production in the presence of 50 μM; (Relic et al., 2009), induces apoptosis at 100 μM; (Hirota et al., 2010), and counteracts the antilipolytic action of insulin if using concentrations above 12.5 μM (Szkudelska et al., 2008).

This is probably due to PPARγ, for which genistein is a direct ligand and activator (Dang et al., 2003). However, the effect of genistein on differentiation of adipocytes has been demonstrated with inconsistent results. This is in part due to contradictory actions of genistein with respect to applied concentrations (Szkudelska et al., 2000; Harmon and Harp, 2001; Linford et al., 2001; Dang et al., 2003; Lee et al., 2006; Relic et al., 2009; Park et al., 2009; Hirota et al., 2010; Cho et al., 2011).

Streptozotocin-diabetic rats, receiving a daily intraperitoneal injection of 1 mg/kg bw, exhibited a hypoglycemic effect (Baluchnejadmojarad and Roghani, 2008). In studies with mice, 2 and 4 g genistein/kg diet (representing an estimated daily intake of about 290 and 500 mg/kg bw) significantly reduced fat pads, ameliorated lipid and cholesterol levels. It also inhibited mRNA expression of PPARγ, leptin and TNFα and enhanced it in the case of PPARα, AMPK, and adiponectin in adipose tissue (Kim et al., 2010). Furthermore, it increases the expression of genes involved in fatty acid oxidation, and, at the same time, triggers expression of uncoupling protein 2, which mediates proton leakage by uncoupling ATP synthesis. This decreased metabolic efficiency may also account for the decreased fat accumulation and weight gain in the animals receiving a daily genistein dose of about 200, 400 or 800 mg/kg bw (Lee et al., 2006). Of note, like resveratrol, genistein administration depleted the ATP level in murine adipocytes (Szkudelska et al., 2011). Recent clinical trials in man attested increased adiponectin levels and a cholesterol and insulin lowering effect, with doses which can easily be obtained by a soy rich diet (Table 1). The $T_{1/2}$ of genistein has been calculated to range between 2.3 and 10.4 h depending on whether free genistein, or

also its glucuronidated and sulfonated metabolites are considered (Burnett et al., 2011), which is in good accordance with reports from Metzner et al. (2009) and Busby et al. (2002). The aglycone is believed to be the biologically active compound in human. However the ingestion of even large genistein doses (16 mg/kg; Busby et al., 2002) only generates a maximal plasma concentration of 0.07–0.4 μM of the unchanged aglycone, which is lower than the values reported for its in vitro effects on adipocytes (12.5–100 μM). Therefore, biological and pharmacological activities (Yuan et al., 2012) of its metabolites likely contribute to genistenin's reported in vivo effects.

2.7. Quercetin

Flavonols are widely distributed in most fruits, vegetables and in onions and quercetin is the most abundant among them. The flavonol quercetin is mainly found in peels and seeds of fruits and vegetable and therefore also rich in olive oil, tea, nuts and red wine. The term is derived from the latin quercus meaning oak, therefore it is also enriched in beverages aged in oak barrels. Thus, its daily dietary consumption in the U.S. is about 30 mg/day (Weldin et al., 2003). Quercetin is known to have multiple biological functions with many beneficial effects on human health, including anti-inflammatory, anti-oxidative and anti-mutagenic activity. Due to these effects, flavonols have been administered in traditional medicine for thousands of years (Middleton et al., 2000). Quercetin is known to activate different kinases which phosphorylate eukaryotic initiation factor 2 thereby stopping cellular translation (Ito et al., 1999). This results in hampered expression of HIF-1α in hypoxic cancer cells, and proves quercetin's anti-cancerogenic role. Interestingly a different outcome has been reported for HIF-1α expression and stability in normoxia instead of hypoxia and with respect to the cell type (Lee and Lee, 2008; Du et al., 2010). Moreover it has been demonstrated that quercetin also induces an accumulation of HIF-1α through chelation of iron, thereby inhibiting the HIF-1 proline hydroxylase and, as a consequence, its further ubiquitination and degradation (Park et al., 2008b). Moreover quercetin has recently been investigated for its curative effect in fibroblasts from Graves' orbitopathy, and thus it has been shown to inhibit inflammation, hyaluronan production, and adipogenesis (Yoon et al., 2011). In murine macrophages, it inhibits the production of TNF-α and NO (Qureshi et al., 2011) and in primary human adipocytes treated with TNF-α, it has been recently shown to prevent insulin resistance and to down-regulate inflammation by attenuating IL-6, IL-1β, IL-8, and MCP-1 expression, even more effectively than resveratrol (Chuang et al., 2010). In addition, quercetin and also resveratrol significantly decreased the secretion of the adipokine visfatin in human adipocytes if treated with 25 μM of the respective phytochemical (Derdemezis et al., 2011). Apart from these effects, quercetin also acts as a pro-apoptotic compound in adipocytes from mice if applied at concentrations above 50 μM: it elevates the expression of caspase-3, -9, Bax, and Bak but declines Bcl-2 protein levels. Similar to other phytochemicals, it also declines the mitochondrial membrane potential (Hsu and Yen, 2006; Ahn et al., 2008). Mechanistically, the up-regulation of AMPK and inhibition of the MAPK pathway by quercetin are the causes for the induced apoptosis in adipocytes and the attenuated adipogenesis. It inhibits JNK- and ERK-phosphorylation and activation and has also been demonstrated to prevent AP-1 and NF-κB activation, the latter by blocking the degradation of IκBα. However, the effect on PPARγ is ambiguous (Ahn et al., 2008; Chuang et al., 2010).

In order to shed light on its molecular properties, Qureshi et al. (2011) recently suggested quercetin as a novel proteasome inhibitor which can affect several proteasomal activities, including the degradation of IκBα. Future studies may further elucidate and complete this mechanistic model.

In vivo studies also attested that quercetin supplementation lessens the inflammatory state in adipose tissue in animal models, as demonstrated for obese Zucker rats given a daily dose of 10 mg/kg bw for 10 weeks. This reduced TNF-α production in the adipose tissue and body weight gain but also improved dyslipidemia, hypertension, and hyperinsulinemia (Rivera et al., 2008). In mice and rats fed a calorie-rich diet the supplementation with quercetin in general lowered levels of circulating glucose, insulin, triglycerides, and cholesterol (Rivera et al., 2008; Wein et al., 2010; Kobori et al., 2011) and enhanced expression and secretion of adiponectin (Rivera et al., 2008; Wein et al., 2010; Kim et al., 2011d). Interestingly quercetin if added to 0.8% to a high fat diet decreased inflammation markers INF-γ, IL-1α, and IL-4 and elevated the energy expenditure in mice (Stewart et al., 2008). In addition, daily feeding with 12.5–25 mg quercetin/kg bw stimulated mitochondrial biogenesis and increased their maximal endurance capacity, further supporting a role of phytochemicals in affecting mitochondrial function (Davis et al., 2009). In human, a daily 1000 mg quercetin supplementation was able to increase mitochondrial DNA and mRNA levels of genes associated with mitochondrial biogenesis (Nieman et al., 2010). Although there are supporting data, demonstrating increased endurance without exercise training in untrained participants after 7 days of daily 1000 mg quercetin (Davis et al., 2010), such metabolic improvements as observed in mice after quercetin treatment, cannot be assigned to humans in general (Cureton et al., 2009; Bigelman et al., 2010; Abbey and Rankin, 2011). According to further human clinical trials, there are no metabolic or thermic effects of quercetin and most studies also failed to elucidate an effect on inflammation (Table 1). Pharmacokinetic analysis determined a $T_{1/2}$ of 3.5 h for unchanged quercetin (Moon et al., 2008) and a poor absorption (Gugler et al., 1975) and its extensive conjugation into sulfate and glucuronide in the liver (Walle et al., 2000). Thus poor results in vivo are probably due to limited bioavailability, whereas knowledge about bioactivity of its metabolites is rather limited. An attempt to rise its bioavailability by cocrystallisation has been recently described (Smith et al., 2011).

Finally, some conflicting or insignificant data (Table 1) can be explained by different health and weight status of study participants and reported large variation with respect to individual plasma concentration of quercetin (Egert et al., 2008; Jin et al., 2010). Furthermore, the apoE polymorphism and other intersubject variabilities influence the response to quercetin (Moon et al., 2008; Egert et al., 2010).

2.8. Combined effects of natural products

Finally, some studies suggest that the anti-inflammatory and antidiabetic effects of these natural products with anti-inflammatory impact could be achieved even if lower doses are used in combination. These combinations synergistically increase their anti-inflammatory activity and thereby the therapeutic effect on inflamed adipose tissue.

Resveratrol and quercetin in combination activated caspase-3 in human pancreatic carcinoma cells (Mouria et al., 2002), suppressed lipid accumulation, decreased the expression of PPARγ, and increased apoptosis in 3T3-L1 mouse adipocytes and the effect was greater than the expected additive response (Yang et al., 2008). Another study showed that genistein and resveratrol in combination had a more potent effect on inhibiting adipogenesis, inducing apoptosis, and promoting lipolysis in 3T3-L1 mouse adipocytes than these compounds alone (Rayalam et al., 2007). It was further reported that the combined treatment of primary human adipocytes with low concentrations of genistein, quercetin and resveratrol inhibited lipid accumulation in maturing adipocytes, decreased cell viability and induced apoptosis, whereas the treatment of the compounds alone had no apoptosis-inducing effect (Park et al., 2008a). Thus, possible toxic effects could be prevented by reducing the dosage of each single natural compound. With respect to the data from clinical studies, a combination of several phytochemicals seems in general to exceed the effect of single administrations. However, patients with T2DM or other inflammatory diseases

would benefit from a more comprehensive knowledge of reasonable combinations of the mentioned phytochemicals. Noteworthy, many natural products contain yet a well-established combination of several phytochemicals like green tea, grapes or other fruits and vegetables.

3. Conclusion

Plenty of health food supplements are available today, however, their molecular targets are still largely unknown and there is a rising number of studies to undertake identification and functional analysis of such active food ingredients. Here we demonstrated that phytochemicals are able to interfere at several points of cellular inflammatory pathways (Fig. 1), although not all in vitro effects have been sufficiently demonstrated to apply also in human adipocytes. Given the proposed action of quercetin as a novel kind of proteasome inhibitor, a more general mode of action may also exist in the context of other phytochemicals. It has been proposed previously that phytochemicals may act by proteasome inhibition, receptor interaction and sirtuin activation (Shay and Banz, 2005). Whereas the latter is controversially discussed, interaction of phytochemicals with receptor PPARγ has been reported for curcumin, capsaicin, catechins, resveratrol, genistein and quercetin, although with contradictory effects, too. Given the safety concerns reported for glitazones (Dormandy et al., 2005; Lubet et al., 2008; Lewis et al., 2011; Mackenzie et al., 2011), a direct activation of PPARγ by phytochemicals should be reconsidered if intended to be used as new therapeutic strategies. Further research may first elucidate and verify their molecular action. Nonetheless, mentioned compounds were all reported to activate AMPK or affect inflammatory cascades via proteasomal activation as well as inactivation of key transcription factors, and this may explain most of the properties attributed to PPARγ interaction. Most likely, there may be several pathways to mediate the effects of each phytochemical on adipocytes.

Of note, these compounds are evolutionarily secondary plant metabolites discouraging plant eaters from grazing as well as fighting against plant pathogens. Therefore, it has been hypothesized more recently that these compounds may act as mitochondrial poisons via inhibiting mitochondrial ATP synthesis, explaining most of their functional properties mentioned above as indirect results due to a lowered ATP level (Zheng and Ramirez, 2000; Hardie, 2011). This hypothesis is substantiated by the findings that resveratrol and genistein, but also catechin, quercetin and curcumin inhibit the respiratory chain and ATP synthetase at the inner mitochondrial membrane (Zini et al., 1999; Zheng and Ramirez, 2000; Szkudelska et al., 2011) and that capsaicin causes a collapse of the mitochondrial membrane potential (Hsu and Yen, 2007). In his unifying hypothesis, Brownlee (2001) suggests that an overproduction of ROS by the mitochondrial electron transfer chain is the link between several independent molecular mechanisms (AGE formation, the polyol and hexosamine pathway flux, PKC activation and NF-κB activation) implicated in diabetic complications. Indeed, interrupting or uncoupling of the proton electrochemical gradient corrected a variety of diabetic phenotypes, and UCP-1 overexpression also provokes PPARγ activation (Brownlee, 2001). Regarding the central role of ROS (Brownlee, 2001) together with the hypoxia-induced ROS production at the mitochondrial electron-transport chain and the subsequent activation of the inflammatory response (Klimova and Chandel, 2008) within the adipose tissue, a more complete understanding of hypoxia-mediated cellular mechanisms as well as phytochemicals with their potential to impact the hypoxic signal at the mitochondrial membrane seems worth a future investigation.

In contrast to white adipose tissue, brown adipose tissue harbors abundant mitochondria and is specialized in the dissipation of energy through the production of heat. This is managed by the action of the uncoupling protein 1 (UCP-1), which bypasses the proton run in the inner mitochondrial membrane. Of interest, a long-term stimulated expression of uncoupling proteins in adipocytes induces a switch of metabolic pathways (Senocak et al., 2007). In addition, there are several studies describing an inverse relation of brown adipose tissue quantity and activity to obesity and age (reviewed in Saely et al., 2010). In this review, numerous examples are given how phytochemicals can modulate inflammatory and metabolic pathways, and some common actions are described for influencing mitochondria. Although white and brown fat cells are probably derived from different progenitors, it cannot be ruled out that they are able to transdifferentiate into each other. An interesting link between brown and white fat is the newly identified hormone irisine, which triggers brown-fat like gene expression in white adipose tissue including UCP-1 upregulation (Boström et al., 2012). This possible relation between natural compounds and the metabolic as well as developmental features of both types of adipocytes should be further addressed in the context of T2DM.

From an evolutionary point of view, in Western diet not only the energy intake but also the dietary composition largely differs from ancient diet, and there was likely a genetic adaptation of ancient human populations to the ingredients too. Because these emerging populations were also separated from each other, naturally they had access to different food supplies. In this context, it is not surprising that people with comparable energy and nutrition intake do not necessarily have the same susceptibility for becoming obese or for developing T2DM. This is underscored in some native populations in the pacific, Australia or the U.S., displaying a disproportionately elevated prevalence of diabetes after switching to Western diet (Zimmet et al., 1990; O'Dea, 1991; Schulz et al., 2006). On the other hand, obesity and the associated diseases like T2DM of today's society are primarily the consequence of a chronic malnutrition which is inadequate to people's environment. Therefore, common genetics but different diet also result in different outcomes as reported for the Pima Indians living in Mexico or the U.S. (Schulz et al., 2006). Moreover, in comparison of ancient or traditionally produced food to modern food, phytochemicals may have been produced formerly in plants to a much higher amount than in today's industrialized and standardized agricultures due to a lack of stress by pathogens or pests. Thus, future studies may also take into account different genetic predispositions for some of these compounds if testing their value as a platform for drug development or diet supplements.

References

Abbey, E.L., Rankin, J.W., 2011. Effect of quercetin supplementation on repeated-sprint performance, xanthine oxidase activity, and inflammation. Int. J. Sport Nutr. Exerc. Metab. 21, 91–96.

Abd El-Aziz, T.A., Mohamed, R.H., Pasha, H.F., Abdel-Aziz, H.R., 2011. Catechin protects against oxidative stress and inflammatory-mediated cardiotoxicity in adriamycin-treated rats. Clin. Exp. Med. http://dx.doi.org/10.1007/s10238-011-0165-2.

Agarwal, A., Prasad, R., Jain, A., 2010. Effect of green tea extract (catechins) in reducing oxidative stress seen in patients of pulmonary tuberculosis on DOTS Cat I regimen. Phytomedicine 17, 23–27.

Ahn, J., Lee, H., Kim, S., Ha, T., 2007. Resveratrol inhibits TNF-alpha-induced changes of adipokines in 3T3-L1 adipocytes. Biochem. Biophys. Res. Commun. 364, 972–977.

Ahn, J., Lee, H., Kim, S., Park, J., Ha, T., 2008. The anti-obesity effect of quercetin is mediated by the AMPK and MAPK signaling pathways. Biochem. Biophys. Res. Commun. 373, 545–549.

Ahn, J., Lee, H., Kim, S., Ha, T., 2010. Curcumin-induced suppression of adipogenic differentiation is accompanied by activation of Wnt/beta-catenin signaling. Am. J. Physiol. Cell Physiol. 298, C1510–C1516.

Ahuja, K.D., Ball, M.J., 2006. Effects of daily ingestion of chilli on serum lipoprotein oxidation in adult men and women. Br. J. Nutr. 96, 239–242.

Ahuja, K.D., Robertson, I.K., Geraghty, D.P., Ball, M.J., 2006. Effects of chili consumption on postprandial glucose, insulin, and energy metabolism. Am. J. Clin. Nutr. 84, 63–69.

Ahuja, K.D., Robertson, I.K., Geraghty, D.P., Ball, M.J., 2007. The effect of 4-week chilli supplementation on metabolic and arterial function in humans. Eur. J. Clin. Nutr. 61, 326–333.

Akiyama, T., Ishida, J., Nakagawa, S., Ogawara, H., Watanabe, S., Itoh, N., Shibuya, M., Fukami, Y., 1987. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J. Biol. Chem. 262, 5592–5595.

Al Amin, Z.M., Thomson, M., Al Qattan, K.K., Peltonen-Shalaby, R., Ali, M., 2006. Anti-diabetic and hypolipidaemic properties of ginger (*Zingiber officinale*) in streptozotocin-induced diabetic rats. Br. J. Nutr. 96, 660–666.

Alcain, F.J., Villalba, J.M., 2009. Sirtuin activators. Expert Opin. Ther. Pat. 19, 403–414.

Alizadeh-Navaei, R., Roozbeh, F., Saravi, M., Pouramir, M., Jalali, F., Moghadamnia, A.A., 2008. Investigation of the effect of ginger on the lipid levels. A double blind controlled clinical trial. Saudi Med. J. 29, 1280–1284.
Alwi, I., Santoso, T., Suyono, S., Sutrisna, B., Suyatna, F.D., Kresno, S.B., Ernie, S., 2008. The effect of curcumin on lipid level in patients with acute coronary syndrome. Acta Med. Indones. 40, 201–210.
Appendino, G., Belcaro, G., Cornelli, U., Luzzi, R., Togni, S., Dugall, M., Cesarone, M.R., Feragalli, B., Ippolito, E., Errichi, B.M., Pellegrini, L., Ledda, A., Ricci, A., Bavera, P., Hosoi, M., Stuard, S., Corsi, M., Errichi, S., Gizzi, G., 2011. Potential role of curcumin phytosome (Meriva) in controlling the evolution of diabetic microangiopathy. A pilot study. Panminerva Med. 53, 43–49.
Asai, A., Miyazawa, T., 2001. Dietary curcuminoids prevent high-fat diet-induced lipid accumulation in rat liver and epididymal adipose tissue. J. Nutr. 131, 2932–2935.
Backesjo, C.M., Li, Y., Lindgren, U., Haldosen, L.A., 2006. Activation of Sirt1 decreases adipocyte formation during osteoblast differentiation of mesenchymal stem cells. J. Bone Miner. Res. 21, 993–1002.
Bae, M.K., Kim, S.H., Jeong, J.W., Lee, Y.M., Kim, H.S., Kim, S.R., Yun, I., Bae, S.K., Kim, K.W., 2006. Curcumin inhibits hypoxia-induced angiogenesis via down-regulation of HIF-1. Oncol. Rep. 15, 1557–1562.
Bae, S.C., Jung, W.J., Lee, E.J., Yu, R., Sung, M.K., 2009. Effects of antioxidant supplements intervention on the level of plasma inflammatory molecules and disease severity of rheumatoid arthritis patients. J. Am. Coll. Nutr. 28, 56–62.
Baer, D.J., Novotny, J.A., Harris, G.K., Stote, K., Clevidence, B., Rumpler, W.V., 2011. Oolong tea does not improve glucose metabolism in non-diabetic adults. Eur. J. Clin. Nutr. 65, 87–93.
Bai, L., Pang, W.J., Yang, Y.J., Yang, G.S., 2008. Modulation of Sirt1 by resveratrol and nicotinamide alters proliferation and differentiation of pig preadipocytes. Mol. Cell. Biochem. 307, 129–140.
Baluchnejadmojarad, T., Roghani, M., 2008. Chronic administration of genistein improves aortic reactivity of streptozotocin-diabetic rats: mode of action. Vascul. Pharmacol. 49, 1–5.
Basu, A., Sanchez, K., Leyva, M.J., Wu, M., Betts, N.M., Aston, C.E., Lyons, T.J., 2010. Green tea supplementation affects body weight, lipids, and lipid peroxidation in obese subjects with metabolic syndrome. J. Am. Coll. Nutr. 29, 31–40.
Basu, A., Du, M., Sanchez, K., Leyva, M.J., Betts, N.M., Blevins, S., Wu, M., Aston, C.E., Lyons, T.J., 2011. Green tea minimally affects biomarkers of inflammation in obese subjects with metabolic syndrome. Nutrition 27, 206–213.
Baum, L., Cheung, S.K., Mok, V.C., Lam, L.C., Leung, V.P., Hui, E., Ng, C.C., Chow, M., Ho, P.C., Lam, S., Woo, J., Chiu, H.F., Goggins, W., Zee, B., Wong, A., Mok, H., Cheng, W.K., Fong, C., Lee, J.S., Chan, M.H., Szeto, S.S., Lui, V.W., Tsoh, J., Kwok, T.C., Chan, I.H., Lam, C.W., 2007. Curcumin effects on blood lipid profile in a 6-month human study. Pharmacol. Res. 56, 509–514.
Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., Pistell, P.J., Poosala, S., Becker, K.G., Boss, O., Gwinn, D., Wang, M., Ramaswamy, S., Fishbein, K.W., Spencer, R.G., Lakatta, E.G., Le Couteur, D., Shaw, R.J., Navas, P., Puigserver, P., Ingram, D.K., de Cabo, R., Sinclair, D.A., 2006. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444, 337–342.
Beattie, J.H., Nicol, F., Gordon, M.J., Reid, M.D., Cantlay, L., Horgan, G.W., Kwun, I.S., Ahn, J.Y., Ha, T.Y., 2011. Ginger phytochemicals mitigate the obesogenic effects of a high-fat diet in mice: a proteomic and biomarker network analysis. Mol. Nutr. Food Res. 55 (Suppl. 2), S203–S213.
Beher, D., Wu, J., Cumine, S., Kim, K.W., Lu, S.C., Atangan, L., Wang, M., 2009. Resveratrol is not a direct activator of SIRT1 enzyme activity. Chem. Biol. Drug Des. 74, 619–624.
Belcaro, G., Cesarone, M.R., Dugall, M., Pellegrini, L., Ledda, A., Grossi, M.G., Togni, S., Appendino, G., 2010. Efficacy and safety of Meriva(R), a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. Altern. Med. Rev. 15, 337–344.
Bès-Houtmann, S., Roche, R., Hoareau, L., Gonthier, M.P., Festy, F., Caillens, H., Gasque, P., Lefebvre, d.C., Cesari, M., 2007. Presence of functional TLR2 and TLR4 on human adipocytes. Histochem. Cell Biol. 127, 131–137.
Bigelman, K.A., Fan, E.H., Chapman, D.P., Freese, E.C., Trilk, J.L., Cureton, K.J., 2010. Effects of six weeks of quercetin supplementation on physical performance in ROTC cadets. Mil. Med. 175, 791–798.
Boots, A.W., Drent, M., de Boer, V.C., Bast, A., Haenen, G.R., 2011. Quercetin reduces markers of oxidative stress and inflammation in sarcoidosis. Clin. Nutr. 30, 506–512.
Borra, M.T., Smith, B.C., Denu, J.M., 2005. Mechanism of human SIRT1 activation by resveratrol. J. Biol. Chem. 280, 17187–17195.
Boschmann, M., Thielecke, F., 2007. The effects of epigallocatechin-3-gallate on thermogenesis and fat oxidation in obese men: a pilot study. J. Am. Coll. Nutr. 26, 389S–395S.
Boström, P., Wu, J., Jedrychowski, M.P., Korde, A., Ye, L., Lo, J.C., Rasbach, K.A., Bostrom, E.A., Choi, J.H., Long, J.Z., Kajimura, S., Zingaretti, M.C., Vind, B.F., Tu, H., Cinti, S., Hojlund, K., Gygi, S.P., Spiegelman, B.M., 2012. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature 481, 463–468.
Brasnyo, P., Molnar, G.A., Mohas, M., Marko, L., Laczy, B., Cseh, J., Mikolas, E., Szijarto, I.A., Merei, A., Halmai, R., Meszaros, L.G., Sumegi, B., Wittmann, I., 2011. Resveratrol improves insulin sensitivity, reduces oxidative stress and activates the Akt pathway in type 2 diabetic patients. Br. J. Nutr. 106, 383–389.
Brossette, T., Hundsdorfer, C., Kroncke, K.D., Sies, H., Stahl, W., 2011. Direct evidence that (−)-epicatechin increases nitric oxide levels in human endothelial cells. Eur. J. Nutr. 50, 595–599.
Brown, A.L., Lane, J., Coverly, J., Stocks, J., Jackson, S., Stephen, A., Bluck, L., Coward, A., Hendrickx, H., 2009. Effects of dietary supplementation with the green tea polyphenol epigallocatechin-3-gallate on insulin resistance and associated metabolic risk factors: randomized controlled trial. Br. J. Nutr. 101, 886–894.
Brown, V.A., Patel, K.R., Viskaduraki, M., Crowell, J.A., Perloff, M., Booth, T.D., Vasilinin, G., Sen, A., Schinas, A.M., Piccirilli, G., Brown, K., Steward, W.P., Gescher, A.J., Brenner, D.E., 2010. Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: safety, pharmacokinetics, and effect on the insulin-like growth factor axis. Cancer Res. 70, 9003–9011.
Brown, A.L., Lane, J., Holyoak, C., Nicol, B., Mayes, A.E., Dadd, T., 2011. Health effects of green tea catechins in overweight and obese men: a randomised controlled cross-over trial. Br. J. Nutr. 106, 1880–1889.
Brownlee, M., 2001. Biochemistry and molecular cell biology of diabetic complications. Nature 414, 813–820.
Burke, B., Giannoudis, A., Corke, K.P., Gill, D., Wells, M., Ziegler-Heitbrock, L., Lewis, C.E., 2003. Hypoxia-induced gene expression in human macrophages: implications for ischemic tissues and hypoxia-regulated gene therapy. Am. J. Pathol. 163, 1233–1243.
Burnett, B.P., Pillai, L., Bitto, A., Squadrito, F., Levy, R.M., 2011. Evaluation of CYP450 inhibitory effects and steady-state pharmacokinetics of genistein in combination with cholecalciferol and citrated zinc bisglycinate in postmenopausal women. Int. J. Womens Health 3, 139–150.
Busby, M.G., Jeffcoat, A.R., Bloedon, L.T., Koch, M.A., Black, T., Dix, K.J., Heizer, W.D., Thomas, B.F., Hill, J.M., Crowell, J.A., Zeisel, S.H., 2002. Clinical characteristics and pharmacokinetics of purified soy isoflavones: single-dose administration to healthy men. Am. J. Clin. Nutr. 75, 126–136.
Calder, P.C., 2005. Polyunsaturated fatty acids and inflammation. Biochem. Soc. Trans. 33, 423–427.
Cao, Z., Fang, J., Xia, C., Shi, X., Jiang, B.H., 2004. trans-3,4,5′-Trihydroxystibene inhibits hypoxia-inducible factor 1alpha and vascular endothelial growth factor expression in human ovarian cancer cells. Clin. Cancer Res. 10, 5253–5263.
Capurso, C., Capurso, A., 2012. From excess adiposity to insulin resistance: the role of free fatty acids. Vascul. Pharmacol. 57, 91–97.
Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., Julius, D., 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 389, 816–824.
Chacon, M.R., Ceperuelo-Mallafre, V., Maymo-Masip, E., Mateo-Sanz, J.M., Arola, L., Guitierrez, C., Fernandez-Real, J.M., Ardevol, A., Simon, I., Vendrell, J., 2009. Grape-seed procyanidins modulate inflammation on human differentiated adipocytes in vitro. Cytokine 47, 137–142.
Chaiyasit, K., Khovidhunkit, W., Wittayalertpanya, S., 2009. Pharmacokinetic and the effect of capsaicin in *Capsicum frutescens* on decreasing plasma glucose level. J. Med. Assoc. Thai. 92, 108–113.
Chan, M.M., Mattiacci, J.A., Hwang, H.S., Shah, A., Fong, D., 2000. Synergy between ethanol and grape polyphenols, quercetin, and resveratrol, in the inhibition of the inducible nitric oxide synthase pathway. Biochem. Pharmacol. 60, 1539–1548.
Charles, C., Yuskavage, J., Carlson, O., John, M., Tagalicud, A.S., Maggio, M., Muller, D.C., Egan, J., Basaria, S., 2009. Effects of high-dose isoflavones on metabolic and inflammatory markers in healthy postmenopausal women. Menopause 16, 395–400.
Chen, S.C., Liu, Y.C., Shyu, K.G., Wang, D.L., 2008. Acute hypoxia to endothelial cells induces activating transcription factor 3 (ATF3) expression that is mediated via nitric oxide. Atherosclerosis 201, 281–288.
Chen, C.J., Yu, W., Fu, Y.C., Wang, X., Li, J.L., Wang, W., 2009a. Resveratrol protects cardiomyocytes from hypoxia-induced apoptosis through the SIRT1-FoxO1 pathway. Biochem. Biophys. Res. Commun. 378, 389–393.
Chen, N., Bezzina, R., Hinch, E., Lewandowski, P.A., Cameron-Smith, D., Mathai, M.L., Jois, M., Sinclair, A.J., Begg, D.P., Wark, J.D., Weisinger, H.S., Weisinger, R.S., 2009b. 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. Nutr. Res. 29, 784–793.
Chen, S., Li, Z., Li, W., Shan, Z., Zhu, W., 2011. Resveratrol inhibits cell differentiation in 3T3-L1 adipocytes via activation of AMPK. Can. J. Physiol. Pharmacol. 89, 793–799.
Cheng, Z., White, M.F., 2011. Targeting Forkhead box O1 from the concept to metabolic diseases: lessons from mouse models. Antioxid. Redox Signal. 14, 649–661.
Cho, J.W., Lee, K.S., Kim, C.W., 2007. Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF-alpha-treated HaCaT cells; NF-kappaB and MAPKs as potential upstream targets. Int. J. Mol. Med. 19, 469–474.
Cho, H.Y., Park, C.M., Kim, M.J., Chinzorig, R., Cho, C.W., Song, Y.S., 2011. Comparative effect of genistein and daidzein on the expression of MCP-1, eNOS, and cell adhesion molecules in TNF-alpha-stimulated HUVECs. Nutr. Res. Pract. 5, 381–388.
Choi, H., Chun, Y.S., Kim, S.W., Kim, M.S., Park, J.W., 2006. Curcumin inhibits hypoxia-inducible factor-1 by degrading aryl hydrocarbon receptor nuclear translocator: a mechanism of tumor growth inhibition. Mol. Pharmacol. 70, 1664–1671.
Choi, S.Y., Kim, S., Son, D., Lee, P., Lee, J., Lee, S., Kim, D.S., Park, Y., Kim, S.Y., 2007. Protective effect of (4-methoxybenzylidene)-(3-methoxynophenyl)amine against neuronal cell death induced by oxygen and glucose deprivation in rat organotypic hippocampal slice culture. Biol. Pharm. Bull. 30, 189–192.
Choi, S.E., Kim, T.H., Yi, S.A., Hwang, Y.C., Hwang, W.S., Choe, S.J., Han, S.J., Kim, H.J., Kim, D.J., Kang, Y., Lee, K.W., 2011. Capsaicin attenuates palmitate-induced expression of macrophage inflammatory protein 1 and interleukin 8 by increasing palmitate oxidation and reducing c-Jun activation in THP-1 (human acute monocytic leukemia cell) cells. Nutr. Res. 31, 468–478.
Chuang, C.C., Martinez, K., Xie, G., Kennedy, A., Bumrungpert, A., Overman, A., Jia, W., McIntosh, M.K., 2010. Quercetin is equally or more effective than resveratrol in attenuating tumor necrosis factor-{alpha}-mediated inflammation and insulin resistance in primary human adipocytes. Am. J. Clin. Nutr. 92, 1511–1521.

Chung, J.Y., Park, J.O., Phyu, H., Dong, Z., Yang, C.S., 2001. Mechanisms of inhibition of the Ras-MAP kinase signaling pathway in 30.7b Ras 12 cells by tea polyphenols (−)-epigallocatechin-3-gallate and theaflavin-3,3′-digallate. FASEB J. 15, 2022–2024.
Corder, R., Mullen, W., Khan, N.Q., Marks, S.C., Wood, E.G., Carrier, M.J., Crozier, A., 2006. Oenology: red wine procyanidins and vascular health. Nature 444, 566.
Costa, C.S., Rohden, F., Hammes, T.O., Margis, R., Bortolotto, J.W., Padoin, A.V., Mottin, C.C., Guaragna, R.M., 2011. Resveratrol upregulated SIRT1, FOXO1, and adiponectin and downregulated PPARgamma1-3 mRNA expression in human visceral adipocytes. Obes. Surg. 21, 356–361.
Cummins, E.P., Taylor, C.T., 2005. Hypoxia-responsive transcription factors. Pflugers Arch. 450, 363–371.
Cureton, K.J., Tomporowski, P.D., Singhal, A., Pasley, J.D., Bigelman, K.A., Lambourne, K., Trilk, J.L., McCully, K.K., Arnaud, M.J., Zhao, Q., 2009. Dietary quercetin supplementation is not ergogenic in untrained men. J. Appl. Physiol. 107, 1095–1104.
Dal Pan, A., Blanc, S., Aujard, F., 2010. Resveratrol suppresses body mass gain in a seasonal non-human primate model of obesity. BMC Physiol. 10, 11.
Danesi, F., Di Nunzio, M., Boschetti, E., Bordoni, A., 2009. Green tea extract selectively activates peroxisome proliferator-activated receptor beta/delta in cultured cardiomyocytes. Br. J. Nutr. 101, 1736–1739.
Dang, Z.C., Audinot, V., Papapoulos, S.E., Boutin, J.A., Lowik, C.W., 2003. Peroxisome proliferator-activated receptor gamma (PPARgamma) as a molecular target for the soy phytoestrogen genistein. J. Biol. Chem. 278, 962–967.
Davis, R.J., 2000. Signal transduction by the JNK group of MAP kinases. Cell 103, 239–252.
Davis, J.M., Murphy, E.A., Carmichael, M.D., Davis, B., 2009. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am. J. Physiol. Regul. Integr. Comp. Physiol. 296, R1071–R1077.
Davis, J.M., Carlstedt, C.J., Chen, S., Carmichael, M.D., Murphy, E.A., 2010. The dietary flavonoid quercetin increases VO(2max) and endurance capacity. Int. J. Sport Nutr. Exerc. Metab. 20, 56–62.
de Boer, V.C., de Goffau, M.C., Arts, I.C., Hollman, P.C., Keijer, J., 2006. SIRT1 stimulation by polyphenols is affected by their stability and metabolism. Mech. Ageing Dev. 127, 618–627.
de Kleijn, M.J., van der Schouw, Y.T., Wilson, P.W., Adlercreutz, H., Mazur, W., Grobbee, D.E., Jacques, P.F., 2001. Intake of dietary phytoestrogens is low in postmenopausal women in the United States: the Framingham study(1–4). J. Nutr. 131, 1826–1832.
Dedov, V.N., Tran, V.H., Duke, C.C., Connor, M., Christie, M.J., Mandadi, S., Roufogalis, B.D., 2002. Gingerols: a novel class of vanilloid receptor (VR1) agonists. Br. J. Pharmacol. 137, 793–798.
Derdemezis, C.S., Kiortsis, D.N., Tsimihodimos, V., Petraki, M.P., Vezyraki, P., Elisaf, M.S., Tselepis, A.D., 2011. Effect of plant polyphenols on adipokine secretion from human SGBS adipocytes. Biochem. Res. Int. 2011, 285618.
Dhillon, N., Aggarwal, B.B., Newman, R.A., Wolff, R.A., Kunnumakkara, A.B., Abbruzzese, J.L., Ng, C.S., Badmaev, V., Kurzrock, R., 2008. Phase II trial of curcumin in patients with advanced pancreatic cancer. Clin. Cancer Res. 14, 4491–4499.
Diepvens, K., Westerterp, K.R., Westerterp-Plantenga, M.S., 2007. Obesity and thermogenesis related to the consumption of caffeine, ephedrine, capsaicin, and green tea. Am. J. Physiol. Regul. Integr. Comp. Physiol. 292, R77–R85.
Domingo, D.S., Camouse, M.M., Hsia, A.H., Matsui, M., Maes, D., Ward, N.L., Cooper, K.D., Baron, E.D., 2010. Anti-angiogenic effects of epigallocatechin-3-gallate in human skin. Int. J. Clin. Exp. Pathol. 3, 705–709.
Dömötör, A., Szolcsányi, J., Mózsik, G., 2006. Capsaicin and glucose absorption and utilization in healthy human subjects. Eur. J. Pharmacol. 534, 280–283.
Donath, M.Y., Shoelson, S.E., 2011. Type 2 diabetes as an inflammatory disease. Nat. Rev. Immunol. 11, 98–107.
Dong, S.Z., Zhao, S.P., Wu, Z.H., Yang, J., Xie, X.Z., Yu, B.L., Nie, S., 2011. Curcumin promotes cholesterol efflux from adipocytes related to PPARgamma-LXRalpha-ABCA1 passway. Mol. Cell. Biochem. 358, 281–285.
Dormandy, J.A., Charbonnel, B., Eckland, D.J., Erdmann, E., Massi-Benedetti, M., Moules, I.K., Skene, A.M., Tan, M.H., Lefebvre, P.J., Murray, G.D., Standl, E., Wilcox, R.G., Wilhelmsen, L., Betteridge, J., Birkeland, K., Golay, A., Heine, R.J., Koranyi, L., Laakso, M., Mokan, M., Norkus, A., Pirags, V., Podar, T., Scheen, A., Scherbaum, W., Schernthaner, G., Schmitz, O., Skrha, J., Smith, U., Taton, J., 2005. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 366, 1279–1289.
Du, G., Lin, H., Wang, M., Zhang, S., Wu, X., Lu, L., Ji, L., Yu, L., 2010. Quercetin greatly improved therapeutic index of doxorubicin against 4T1 breast cancer by its opposing effects on HIF-1alpha in tumor and normal cells. Cancer Chemother. Pharmacol. 65, 277–287.
Dulloo, A.G., Seydoux, J., Girardier, L., Chantre, P., Vandermander, J., 2000. Green tea and thermogenesis: interactions between catechin-polyphenols, caffeine and sympathetic activity. Int. J. Obes. Relat. Metab. Disord. 24, 252–258.
Duvoix, A., Blasius, R., Delhalle, S., Schnekenburger, M., Morceau, F., Henry, E., Dicato, M., Diederich, M., 2005. Chemopreventive and therapeutic effects of curcumin. Cancer Lett. 223, 181–190.
Dyerberg, J., Schmidt, E.B., 1989. n − 3 fatty acids and cardiovascular disease—observations generated by studies in Greenland Eskimos. Wien. Klin. Wochenschr. 101, 277–282.
Eaton, S.B., Konner, M., 1985. Paleolithic nutrition. A consideration of its nature and current implications. N. Engl. J. Med. 312, 283–289.
Ebbesson, S.O., Risica, P.M., Ebbesson, L.O., Kennish, J.M., Tejero, M.E., 2005. Omega-3 fatty acids improve glucose tolerance and components of the metabolic syndrome in Alaskan Eskimos: the Alaska Siberia project. Int. J. Circumpolar Health 64, 396–408.
Ebbesson, S.O., Tejero, M.E., Lopez-Alvarenga, J.C., Harris, W.S., Ebbesson, L.O., Devereux, R.B., MacCluer, J.W., Wenger, C., Laston, S., Fabsitz, R.R., Howard, B.V., Comuzzie, A.G., 2010. Individual saturated fatty acids are associated with different components of insulin resistance and glucose metabolism: the GOCADAN study. Int. J. Circumpolar Health 69, 344–351.
Egert, S., Wolffram, S., Bosy-Westphal, A., Boesch-Saadatmandi, C., Wagner, A.E., Frank, J., Rimbach, G., Mueller, M.J., 2008. Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J. Nutr. 138, 1615–1621.
Egert, S., Bosy-Westphal, A., Seiberl, J., Kurbitz, C., Settler, U., Plachta-Danielzik, S., Wagner, A.E., Frank, J., Schrezenmeir, J., Rimbach, G., Wolffram, S., Muller, M.J., 2009. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br. J. Nutr. 102, 1065–1074.
Egert, S., Boesch-Saadatmandi, C., Wolffram, S., Rimbach, G., Muller, M.J., 2010. Serum lipid and blood pressure responses to quercetin vary in overweight patients by apolipoprotein E genotype. J. Nutr. 140, 278–284.
Egert, S., Rimbach, G., Muller, M.J., 2011. No evidence for a thermic effect of the dietary flavonol quercetin: a pilot study in healthy normal-weight women. Eur. J. Appl. Physiol. 111, 869–873.
Ejaz, A., Wu, D., Kwan, P., Meydani, M., 2009. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. J. Nutr. 139, 919–925.
Eldershaw, T.P., Colquhoun, E.Q., Dora, K.A., Peng, Z.C., Clark, M.G., 1992. Pungent principles of ginger (*Zingiber officinale*) are thermogenic in the perfused rat hindlimb. Int. J. Obes. Relat. Metab. Disord. 16, 755–763.
Erickson, J.T., Millhorn, D.E., 1994. Hypoxia and electrical stimulation of the carotid sinus nerve induce Fos-like immunoreactivity within catecholaminergic and serotoninergic neurons of the rat brainstem. J. Comp. Neurol. 348, 161–182.
Famulla, S., Horrighs, A., Cramer, A., Sell, H., Eckel, J., 2011. Hypoxia reduces the response of human adipocytes towards TNFalpha resulting in reduced NF-kappaB signaling and MCP-1 secretion. Int. J. Obes. 36, 986–992 (Lond).
Fandrey, J., Gorr, T.A., Gassmann, M., 2006. Regulating cellular oxygen sensing by hydroxylation. Cardiovasc. Res. 71, 642–651.
Fischer-Posovszky, P., Kukulus, V., Tews, D., Unterkircher, T., Debatin, K.M., Fulda, S., Wabitsch, M., 2010. Resveratrol regulates human adipocyte number and function in a Sirt1-dependent manner. Am. J. Clin. Nutr. 92, 5–15.
Fleischmann, E., Kurz, A., Niedermayr, M., Schebesta, K., Kimberger, O., Sessler, D.I., Kabon, B., Prager, G., 2005. Tissue oxygenation in obese and non-obese patients during laparoscopy. Obes. Surg. 15, 813–819.
Floyd, Z.E., Wang, Z.Q., Kilroy, G., Cefalu, W.T., 2008. Modulation of peroxisome proliferator-activated receptor gamma stability and transcriptional activity in adipocytes by resveratrol. Metabolism 57, S32–S38.
Fotsis, T., Pepper, M., Adlercreutz, H., Hase, T., Montesano, R., Schweigerer, L., 1995. Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. J. Nutr. 125, 790S–797S.
Fukino, Y., Ikeda, A., Maruyama, K., Aoki, N., Okubo, T., Iso, H., 2008. Randomized controlled trial for an effect of green tea-extract powder supplementation on glucose abnormalities. Eur. J. Clin. Nutr. 62, 953–960.
Geiger, K., Leiherer, A., Muendlein, A., Stark, N., Geller-Rhomberg, S., Saely, C.H., Wabitsch, M., Fraunberger, P., Drexel, H., 2011a. Identification of hypoxia-induced genes in human SGBS adipocytes by microarray analysis. PLoS One 6, e26465.
Geiger, K., Muendlein, A., Stark, N., Saely, C.H., Wabitsch, M., Fraunberger, P., Drexel, H., 2011b. Hypoxia induces apelin expression in human adipocytes. Horm. Metab. Res. 43, 380–385.
Ghanim, H., Sia, C.L., Abuaysheh, S., Korzeniewski, K., Patnaik, P., Marumganti, A., Chaudhuri, A., Dandona, P., 2010. An antiinflammatory and reactive oxygen species suppressive effects of an extract of *Polygonum cuspidatum* containing resveratrol. J. Clin. Endocrinol. Metab. 95, E1–E8.
Gonzalez-Muniesa, P., de Oliveira, C., Perez, d.H., Thompson, M.P., Trayhurn, P., 2011. Fatty acids and hypoxia stimulate the expression and secretion of the adipokine ANGPTL4 (angiopoietin-like protein 4/fasting-induced adipose factor) by human adipocytes. J. Nutrigenet. Nutrigenomics 4, 146–153.
Gresele, P., Pignatelli, P., Guglielmini, G., Carnevale, R., Mezzasoma, A.M., Ghiselli, A., Momi, S., Violi, F., 2008. Resveratrol, at concentrations attainable with moderate wine consumption, stimulates human platelet nitric oxide production. J. Nutr. 138, 1602–1608.
Guarente, L., 2006. Sirtuins as potential targets for metabolic syndrome. Nature 444, 868–874.
Guevara-Aguirre, J., Balasubramanian, P., Guevara-Aguirre, M., Wei, M., Madia, F., Cheng, C.W., Hwang, D., Martin-Montalvo, A., Saavedra, J., Ingles, S., de Cabo, R., Cohen, P., Longo, V.D., 2011. Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci. Transl. Med. 3, 70ra13.
Gugler, R., Leschik, M., Dengler, H.J., 1975. Disposition of quercetin in man after single oral and intravenous doses. Eur. J. Clin. Pharmacol. 9, 229–234.
Halberg, N., Khan, T., Trujillo, M.E., Wernstedt-Asterholm, I., Attie, A.D., Sherwani, S., Wang, Z.V., Landskroner-Eiger, S., Dineen, S., Magalang, U.J., Brekken, R.A., Scherer, P.E., 2009. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. Mol. Cell. Biol. 29, 4467–4483.
Hara, Y., Fujino, M., Adachi, K., Li, X.K., 2006. The reduction of hypoxia-induced and reoxygenation-induced apoptosis in rat islets by epigallocatechin gallate. Transplant. Proc. 38, 2722–2725.
Hardie, D.G., 2011. Sensing of energy and nutrients by AMP-activated protein kinase. Am. J. Clin. Nutr. 93, 891S–896S.
Harmon, A.W., Harp, J.B., 2001. Differential effects of flavonoids on 3T3-L1 adipogenesis and lipolysis. Am. J. Physiol. Cell Physiol. 280, C807–C813.
Haxhiu, M.A., Strohl, K.P., Cherniack, N.S., 1995. The N-methyl-D-aspartate receptor pathway is involved in hypoxia-induced c-Fos protein expression in the rat nucleus of the solitary tract. J. Auton. Nerv. Syst. 55, 65–68.

He, Z.Y., Shi, C.B., Wen, H., Li, F.L., Wang, B.L., Wang, J., 2011. Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Invest. 29, 208–213.
Heinz, S.A., Henson, D.A., Nieman, D.C., Austin, M.D., Jin, F., 2010. A 12-week supplementation with quercetin does not affect natural killer cell activity, granulocyte oxidative burst activity or granulocyte phagocytosis in female human subjects. Br. J. Nutr. 104, 849–857.
Hill, A.M., Coates, A.M., Buckley, J.D., Ross, R., Thielecke, F., Howe, P.R., 2007. Can EGCG reduce abdominal fat in obese subjects? J. Am. Coll. Nutr. 26, 396S–402S.
Hirota, K., Morikawa, K., Hanada, H., Nonaka, M., Nakajima, Y., Kobayashi, M., Nakajima, R., 2010. Effect of genistein and daidzein on the proliferation and differentiation of human preadipocyte cell line. J. Agric. Food Chem. 58, 5821–5827.
Hollenberg, K., 2006. Vascular action of cocoa flavanols in humans: the roots of the story. J. Cardiovasc. Pharmacol. 47 (Suppl. 2), S99–S102.
Holmes-McNary, M., Baldwin Jr., A.S., 2000. Chemopreventive properties of trans-resveratrol are associated with inhibition of activation of the IkappaB kinase. Cancer Res. 60, 3477–3483.
Hong, M.H., Kim, M.H., Chang, H.J., Kim, N.H., Shin, B.A., Ahn, B.W., Jung, Y.D., 2007. (−)-Epigallocatechin-3-gallate inhibits monocyte chemotactic protein-1 expression in endothelial cells via blocking NF-kappaB signaling. Life Sci. 80, 1957–1965.
Horn-Ross, P.L., John, E.M., Lee, M., Stewart, S.L., Koo, J., Sakoda, L.C., Shiau, A.C., Goldstein, J., Davis, P., Perez-Stable, E.J., 2001. Phytoestrogen consumption and breast cancer risk in a multiethnic population: the Bay Area Breast Cancer Study. Am. J. Epidemiol. 154, 434–441.
Hosogai, N., Fukuhara, A., Oshima, K., Miyata, Y., Tanaka, S., Segawa, K., Furukawa, S., Tochino, Y., Komuro, R., Matsuda, M., Shimomura, I., 2007. Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation. Diabetes 56, 901–911.
Howitz, K.T., Bitterman, K.J., Cohen, H.Y., Lamming, D.W., Lavu, S., Wood, J.G., Zipkin, R.E., Chung, P., Kisielewski, A., Zhang, L.L., Scherer, B., Sinclair, D.A., 2003. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. Nature 425, 191–196.
Hsu, C.L., Yen, G.C., 2006. Induction of cell apoptosis in 3T3-L1 pre-adipocytes by flavonoids is associated with their antioxidant activity. Mol. Nutr. Food Res. 50, 1072–1079.
Hsu, C.L., Yen, G.C., 2007. Effects of capsaicin on induction of apoptosis and inhibition of adipogenesis in 3T3-L1 cells. J. Agric. Food Chem. 55, 1730–1736.
Hsu, C.H., Liao, Y.L., Lin, S.C., Tsai, T.H., Huang, C.J., Chou, P., 2011. Does supplementation with green tea extract improve insulin resistance in obese type 2 diabetics? A randomized, double-blind, and placebo-controlled clinical trial. Altern. Med. Rev. 16, 157–163.
Hwang, J.T., Park, I.J., Shin, J.I., Lee, Y.K., Lee, S.K., Baik, H.W., Ha, J., Park, O.J., 2005. Genistein, EGCG, and capsaicin inhibit adipocyte differentiation process via activating AMP-activated protein kinase. Biochem. Biophys. Res. Commun. 338, 694–699.
Hwang, J.T., Kim, S., Choi, S.Y., 2010. Inhibitory effect of (E)-1,2-di(3,5-dimethoxyphenyl) ethene on 3T3-L1 adiopocyte differentiation. Pharmazie 65, 903–905.
Ikonomov, O.C., Sbrissa, D., Mlak, K., Shisheva, A., 2002. Requirement for PIKfyve enzymatic activity in acute and long-term insulin cellular effects. Endocrinology 143, 4742–4754.
Inami, S., Takano, M., Yamamoto, M., Murakami, D., Tajika, K., Yodogawa, K., Yokoyama, S., Ohno, N., Ohba, T., Sano, J., Ibuki, C., Seino, Y., Mizuno, K., 2007. Tea catechin consumption reduces circulating oxidized low-density lipoprotein. Int. Heart J. 48, 725–732.
Isa, Y., Miyakawa, Y., Yanagisawa, M., Goto, T., Kang, M.S., Kawada, T., Morimitsu, Y., Kubota, K., Tsuda, T., 2008. 6-Shogaol and 6-gingerol, the pungent of ginger, inhibit TNF-alpha mediated downregulation of adiponectin expression via different mechanisms in 3T3-L1 adipocytes. Biochem. Biophys. Res. Commun. 373, 429–434.
Islam, M.S., Choi, H., 2008. Comparative effects of dietary ginger (*Zingiber officinale*) and garlic (*Allium sativum*) investigated in a type 2 diabetes model of rats. J. Med. Food 11, 152–159.
Ito, T., Warnken, S.P., May, W.S., 1999. Protein synthesis inhibition by flavonoids: roles of eukaryotic initiation factor 2alpha kinases. Biochem. Biophys. Res. Commun. 265, 589–594.
Jacob, A., Wu, R., Zhou, M., Wang, P., 2007. Mechanism of the anti-inflammatory effect of curcumin: PPAR-gamma activation. PPAR Res. 89369.
Jang, E.M., Choi, M.S., Jung, U.J., Kim, M.J., Kim, H.J., Jeon, S.M., Shin, S.K., Seong, C.N., Lee, M.K., 2008. Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat-fed hamsters. Metabolism 57, 1576–1583.
Jiang, H., Xie, Z., Koo, H.J., McLaughlin, S.P., Timmermann, B.N., Gang, D.R., 2006. Metabolic profiling and phylogenetic analysis of medicinal Zingiber species: tools for authentication of ginger (*Zingiber officinale* Rosc). Phytochemistry 67, 1673–1685.
Jin, F., Nieman, D.C., Shanely, R.A., Knab, A.M., Austin, M.D., Sha, W., 2010. The variable plasma quercetin response to 12-week quercetin supplementation in humans. Eur. J. Clin. Nutr. 64, 692–697.
Jing, Y., Han, G., Hu, Y., Bi, Y., Li, L., Zhu, D., 2009. Tea consumption and risk of type 2 diabetes: a meta-analysis of cohort studies. J. Gen. Intern. Med. 24, 557–562.
Jorgensen, M.E., Borch-Johnsen, K., Bjerregaard, P., 2006. Lifestyle modifies obesity-associated risk of cardiovascular disease in a genetically homogeneous population. Am. J. Clin. Nutr. 84, 29–36.
Jutooru, I., Chadalapaka, G., Lei, P., Safe, S., 2010. Inhibition of NFkappaB and pancreatic cancer cell and tumor growth by curcumin is dependent on specificity protein down-regulation. J. Biol. Chem. 285, 25332–25344.
Kabon, B., Nagele, A., Reddy, D., Eagon, C., Fleshman, J.W., Sessler, D.I., Kurz, A., 2004. Obesity decreases perioperative tissue oxygenation. Anesthesiology 100, 274–280.
Kaeberlein, M., McDonagh, T., Heltweg, B., Hixon, J., Westman, E.A., Caldwell, S.D., Napper, A., Curtis, R., DiStefano, P.S., Fields, S., Bedalov, A., Kennedy, B.K., 2005. Substrate-specific activation of sirtuins by resveratrol. J. Biol. Chem. 280, 17038–17045.
Kalpravidh, R.W., Siritanaratkul, N., Insain, P., Charoensakdi, R., Panichkul, N., Hatairaktham, S., Srichairatanakool, S., Phisalaphong, C., Rachmilewitz, E., Fucharoen, S., 2010. Improvement in oxidative stress and antioxidant parameters in beta-thalassemia/Hb E patients treated with curcuminoids. Clin. Biochem. 43, 424–429.
Kanai, M., Yoshimura, K., Asada, M., Imaizumi, A., Suzuki, C., Matsumoto, S., Nishimura, T., Mori, Y., Masui, T., Kawaguchi, Y., Yanagihara, K., Yazumi, S., Chiba, T., Guha, S., Aggarwal, B.B., 2011. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. Cancer Chemother. Pharmacol. 68, 157–164.
Kanai, M., Imaizumi, A., Otsuka, Y., Sasaki, H., Hashiguchi, M., Tsujiko, K., Matsumoto, S., Ishiguro, H., Chiba, T., 2012. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother. Pharmacol. 69, 65–70.
Kang, J.H., Kim, C.S., Han, I.S., Kawada, T., Yu, R., 2007. Capsaicin, a spicy component of hot peppers, modulates adipokine gene expression and protein release from obese-mouse adipose tissues and isolated adipocytes, and suppresses the inflammatory responses of adipose tissue macrophages. FEBS Lett. 581, 4389–4396.
Kang, J.H., Tsuyoshi, G., Le Ngoc, H., Kim, H.M., Tu, T.H., Noh, H.J., Kim, C.S., Choe, S.Y., Kawada, T., Yoo, H., Yu, R., 2011. Dietary capsaicin attenuates metabolic dysregulation in genetically obese diabetic mice. J. Med. Food 14, 310–315.
Kawada, T., Hagihara, K., Iwai, K., 1986a. Effects of capsaicin on lipid metabolism in rats fed a high fat diet. J. Nutr. 116, 1272–1278.
Kawada, T., Watanabe, T., Takaishi, T., Tanaka, T., Iwai, K., 1986b. Capsaicin-induced beta-adrenergic action on energy metabolism in rats: influence of capsaicin on oxygen consumption, the respiratory quotient, and substrate utilization. Proc. Soc. Exp. Biol. Med. 183, 250–256.
Kawai, T., Akira, S., 2007. TLR signaling. Semin. Immunol. 19, 24–32.
Kean, B.H., 1944. The blood presure of the Cuna Indians. Am. J. Trop. Med. Hyg. 24, 341–343.
Kennedy, A., Overman, A., Lapoint, K., Hopkins, R., West, T., Chuang, C.C., Martinez, K., Bell, D., McIntosh, M., 2009. Conjugated linoleic acid-mediated inflammation and insulin resistance in human adipocytes are attenuated by resveratrol. J. Lipid Res. 50, 225–232.
Khajehdehi, P., Pakfetrat, M., Javidnia, K., Azad, F., Malekmakan, L., Nasab, M.H., Dehghanzadeh, G., 2011. Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-beta and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. Scand. J. Urol. Nephrol. 45, 365–370.
Khokhar, S., Magnusdottir, S.G., 2002. Total phenol, catechin, and caffeine contents of teas commonly consumed in the United kingdom. J. Agric. Food Chem. 50, 565–570.
Kim, H., Sakamoto, K., 2011. (−)-Epigallocatechin gallate suppresses adipocyte differentiation through the MEK/ERK and PI3K/AKT pathways. Cell Biol. Int. 36, 147–153.
Kim, C.S., Kawada, T., Kim, B.S., Han, I.S., Choe, S.Y., Kurata, T., Yu, R., 2003. Capsaicin exhibits anti-inflammatory property by inhibiting IkB-a degradation in LPS-stimulated peritoneal macrophages. Cell. Signal. 15, 299–306.
Kim, Y.A., Choi, B.T., Lee, Y.T., Park, D.I., Rhee, S.H., Park, K.Y., Choi, Y.H., 2004. Resveratrol inhibits cell proliferation and induces apoptosis of human breast carcinoma MCF-7 cells. Oncol. Rep. 11, 441–446.
Kim, S.O., Kundu, J.K., Shin, Y.K., Park, J.H., Cho, M.H., Kim, T.Y., Surh, Y.J., 2005. [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin. Oncogene 24, 2558–2567.
Kim, M.H., Kang, K.S., Lee, Y.S., 2010. The inhibitory effect of genistein on hepatic steatosis is linked to visceral adipocyte metabolism in mice with diet-induced non-alcoholic fatty liver disease. Br. J. Nutr. 104, 1333–1342.
Kim, C.Y., Bordenave, N., Ferruzzi, M.G., Safavy, A., Kim, K.H., 2011a. Modification of curcumin with polyethylene glycol enhances the delivery of curcumin in preadipocytes and its antiadipogenic property. J. Agric. Food Chem. 59, 1012–1019.
Kim, C.Y., Le, T.T., Chen, C., Cheng, J.X., Kim, K.H., 2011b. Curcumin inhibits adipocyte differentiation through modulation of mitotic clonal expansion. J. Nutr. Biochem. 22, 910–920.
Kim, J.H., Park, S.H., Nam, S.W., Kwon, H.J., Kim, B.W., Kim, W.J., Choi, Y.H., 2011c. Curcumin stimulates proliferation, stemness acting signals and migration of 3T3-L1 preadipocytes. Int. J. Mol. Med. 28, 429–435.
Kim, O.Y., Lee, S.M., Do, H., Moon, J., Lee, K.H., Cha, Y.J., Shin, M.J., 2011d. Influence of quercetin-rich onion peel extracts on adipokine expression in the visceral adipose tissue of rats. Phytother. Res. 26, 432–437.
Kintscher, U., Hartge, M., Hess, K., Foryst-Ludwig, A., Clemenz, M., Wabitsch, M., Fischer-Posovszky, P., Barth, T.F., Dragun, D., Skurk, T., Hauner, H., Bluher, M., Unger, T., Wolf, A.M., Knippschild, U., Hombach, V., Marx, N., 2008. T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance. Arterioscler. Thromb. Vasc. Biol. 28, 1304–1310.
Kipp, J.L., Ramirez, V.D., 2001. Effect of estradiol, diethylstilbestrol, and resveratrol on F0F1-ATPase activity from mitochondrial preparations of rat heart, liver, and brain. Endocrine 15, 165–175.
Klimova, T., Chandel, N.S., 2008. Mitochondrial complex III regulates hypoxic activation of HIF. Cell Death Differ. 15, 660–666.
Knab, A.M., Shanely, R.A., Henson, D.A., Jin, F., Heinz, S.A., Austin, M.D., Nieman, D.C., 2011. Influence of quercetin supplementation on disease risk factors in community-dwelling adults. J. Am. Diet. Assoc. 111, 542–549.
Kobori, M., Masumoto, S., Akimoto, Y., Oike, H., 2011. Chronic dietary intake of quercetin alleviates hepatic fat accumulation associated with consumption of a Western-style diet in C57/BL6J mice. Mol. Nutr. Food Res. 55, 530–540.

Konrad, M., Nieman, D.C., Henson, D.A., Kennerly, K.M., Jin, F., Wallner-Liebmann, S.J., 2011. The acute effect of ingesting a quercetin-based supplement on exercise-induced inflammation and immune changes in runners. Int. J. Sport Nutr. Exerc. Metab. 21, 338–346.
Ku, Y., Choi, S., 1990. The scientific technology of kimchi. The Composition of Foods. Korean Institute of Food Development, Seoul, Korea, pp. 33–34.
Kyriakis, J.M., Avruch, J., 2001. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol. Rev. 81, 807–869.
Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, P., Geny, B., Laakso, M., Puigserver, P., Auwerx, J., 2006. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 127, 1109–1122.
Lazarevic, B., Boezelijn, G., Diep, L.M., Kvernrod, K., Ogren, O., Ramberg, H., Moen, A., Wessel, N., Berg, R.E., Egge-Jacobsen, W., Hammarstrom, C., Svindland, A., Kucuk, O., Saatcioglu, F., Tasken, K.A., Karlsen, S.J., 2011. Efficacy and safety of short-term genistein intervention in patients with localized prostate cancer prior to radical prostatectomy: a randomized, placebo-controlled, double-blind Phase 2 clinical trial. Nutr. Cancer 63, 889–898.
Lee, M.S., Kim, Y., 2009. (−)-Epigallocatechin-3-gallate enhances uncoupling protein 2 gene expression in 3T3-L1 adipocytes. Biosci. Biotechnol. Biochem. 73, 434–436.
Lee, D.H., Lee, Y.J., 2008. Quercetin suppresses hypoxia-induced accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha) through inhibiting protein synthesis. J. Cell. Biochem. 105, 546–553.
Lee, J.Y., Plakidas, A., Lee, W.H., Heikkinen, A., Chanmugam, P., Bray, G., Hwang, D.H., 2003a. Differential modulation of Toll-like receptors by fatty acids: preferential inhibition by n-3 polyunsaturated fatty acids. J. Lipid Res. 44, 479–486.
Lee, Y.H., Giraud, J., Davis, R.J., White, M.F., 2003b. c-Jun N-terminal kinase (JNK) mediates feedback inhibition of the insulin signaling cascade. J. Biol. Chem. 278, 2896–2902.
Lee, Y.M., Choi, J.S., Kim, M.H., Jung, M.H., Lee, Y.S., Song, J., 2006. Effects of dietary genistein on hepatic lipid metabolism and mitochondrial function in mice fed high-fat diets. Nutrition 22, 956–964.
Lee, H., Lee, Y.J., Choi, H., Ko, E.H., Kim, J.W., 2009a. Reactive oxygen species facilitate adipocyte differentiation by accelerating mitotic clonal expansion. J. Biol. Chem. 284, 10601–10609.
Lee, Y.K., Lee, W.S., Hwang, J.T., Kwon, D.Y., Surh, Y.J., Park, O.J., 2009b. Curcumin exerts antidifferentiation effect through AMPKalpha-PPAR-gamma in 3T3-L1 adipocytes and antiproliferatory effect through AMPKalpha-COX-2 in cancer cells. J. Agric. Food Chem. 57, 305–310.
Lee, M.S., Kim, C.T., Kim, I.H., Kim, Y., 2011. Effects of capsaicin on lipid catabolism in 3T3-L1 adipocytes. Phytother. Res. 25, 935–939.
Leiro, J., Alvarez, E., Garcia, D., Orallo, F., 2002. Resveratrol modulates rat macrophage functions. Int. Immunopharmacol. 2, 767–774.
Leiro, J., Alvarez, E., Arranz, J.A., Laguna, R., Uriarte, E., Orallo, F., 2004. Effects of cis-resveratrol on inflammatory murine macrophages: antioxidant activity and down-regulation of inflammatory genes. J. Leukoc. Biol. 75, 1156–1165.
Lejeune, M.P., Kovacs, E.M., Westerterp-Plantenga, M.S., 2003. Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. Br. J. Nutr. 90, 651–659.
Leone, M., Zhai, D., Sareth, S., Kitada, S., Reed, J.C., Pellecchia, M., 2003. Cancer prevention by tea polyphenols is linked to their direct inhibition of antiapoptotic Bcl-2-family proteins. Cancer Res. 63, 8118–8121.
Lewis, J.D., Ferrara, A., Peng, T., Hedderson, M., Bilker, W.B., Quesenberry Jr., C.P., Vaughn, D.J., Nessel, L., Selby, J., Strom, B.L., 2011. Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes Care 34, 916–922.
Li, Z., Ya, K., Xiao-Mei, W., Lei, Y., Yang, L., Ming, Q.Z., 2008. Ginkgolides protect PC12 cells against hypoxia-induced injury by p42/p44 MAPK pathway-dependent upregulation of HIF-1alpha expression and HIF-1DNA-binding activity. J. Cell. Biochem. 103, 564–575.
Li, Y., Zhang, J.F., Zhang, Y.M., Ma, X.B., 2009. The protective effect of genistein postconditioning on hypoxia/reoxygenation-induced injury in human gastric epithelial cells. Acta Pharmacol. Sin. 30, 576–581.
Lichtenstein, L., Mattijssen, F., de Wit, N.J., Georgiadi, A., Hooiveld, G.J., van der, M.R., He, Y., Qi, L., Koster, A., Tamsma, J.T., Tan, N.S., Muller, M., Kersten, S., 2010. Angptl4 protects against severe proinflammatory effects of saturated fat by inhibiting fatty acid uptake into mesenteric lymph node macrophages. Cell Metab. 12, 580–592.
Lin, Y.L., Lin, J.K., 1997. (−)-Epigallocatechin-3-gallate blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of transcription factor nuclear factor-kappaB. Mol. Pharmacol. 52, 465–472.
Lin, S.K., Shun, C.T., Kok, S.H., Wang, C.C., Hsiao, T.Y., Liu, C.M., 2008. Hypoxia-stimulated vascular endothelial growth factor production in human nasal polyp fibroblasts: effect of epigallocatechin-3-gallate on hypoxia-inducible factor-1 alpha synthesis. Arch. Otolaryngol. Head Neck Surg. 134, 522–527.
Linford, N.J., Yang, Y., Cook, D.G., Dorsa, D.M., 2001. Neuronal apoptosis resulting from high doses of the isoflavone genistein: role for calcium and p42/44 mitogen-activated protein kinase. J. Pharmacol. Exp. Ther. 299, 67–75.
Liu, J., Divoux, A., Sun, J., Zhang, J., Clement, K., Glickman, J.N., Sukhova, G.K., Wolters, P.J., Du, J., Gorgun, C.Z., Doria, A., Libby, P., Blumberg, R.S., Kahn, B.B., Hotamisligil, G.S., Shi, G.P., 2009. Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice. Nat. Med. 15, 940–945.
Llaneza, P., Gonzalez, C., Fernandez-Inarrea, J., Alonso, A., Diaz, F., Arnott, I., Ferrer-Barriendos, J., 2011. Soy isoflavones, diet and physical exercise modify serum cytokines in healthy obese postmenopausal women. Phytomedicine 18, 245–250.
Lonac, M.C., Richards, J.C., Schweder, M.M., Johnson, T.K., Bell, C., 2011. Influence of short-term consumption of the caffeine-free, epigallocatechin-3-gallate supplement, Teavigo, on resting metabolism and the thermic effect of feeding. Obesity (Silver Spring) 19, 298–304.
Lu, J., Guan, S., Shen, X., Qian, W., Huang, G., Deng, X., Xie, G., 2011. Immunosuppressive activity of 8-gingerol on immune responses in mice. Molecules 16, 2636–2645.
Lubet, R.A., Fischer, S.M., Steele, V.E., Juliana, M.M., Desmond, R., Grubbs, C.J., 2008. Rosiglitazone, a PPAR gamma agonist: potent promoter of hydroxybutyl(butyl)nitrosamine-induced urinary bladder cancers. Int. J. Cancer 123, 2254–2259.
Ludy, M.J., Mattes, R.D., 2011. The effects of hedonically acceptable red pepper doses on thermogenesis and appetite. Physiol. Behav. 102, 251–258.
Macarulla, M.T., Alberdi, G., Gomez, S., Tueros, I., Bald, C., Rodriguez, V.M., Martinez, J.A., Portillo, M.P., 2009. Effects of different doses of resveratrol on body fat and serum parameters in rats fed a hypercaloric diet. J. Physiol. Biochem. 65, 369–376.
Mackenzie, T., Leary, L., Brooks, W.B., 2007. The effect of an extract of green and black tea on glucose control in adults with type 2 diabetes mellitus: double-blind randomized study. Metabolism 56, 1340–1344.
Mackenzie, T., Zens, M.S., Ferrara, A., Schned, A., Karagas, M.R., 2011. Diabetes and risk of bladder cancer: evidence from a case–control study in New England. Cancer 117, 1552–1556.
Mader, I., Wabitsch, M., Debatin, K.M., Fischer-Posovszky, P., Fulda, S., 2010. Identification of a novel proapoptotic function of resveratrol in fat cells: SIRT1-independent sensitization to TRAIL-induced apoptosis. FASEB J. 24, 1997–2009.
Marini, H., Bitto, A., Altavilla, D., Burnett, B.P., Polito, F., Di, S.V., Minutoli, L., Atteritano, M., Levy, R.M., Frisina, N., Mazzaferro, S., Frisina, A., D'Anna, R., Cancellieri, F., Cannata, M.L., Corrado, F., Lubrano, C., Marini, R., Adamo, E.B., Squadrito, F., 2010. Efficacy of genistein aglycone on some cardiovascular risk factors and homocysteine levels: a follow-up study. Nutr. Metab. Cardiovasc. Dis. 20, 332–340.
Mark, L., Nikfardjam, M.S., Avar, P., Ohmacht, R., 2005. A validated HPLC method for the quantitative analysis of trans-resveratrol and trans-piceid in Hungarian wines. J. Chromatogr. Sci. 43, 445–449.
Markovits, J., Linassier, C., Fosse, P., Couprie, J., Pierre, J., Jacquemin-Sablon, A., Saucier, J.M., Le Pecq, J.B., Larsen, A.K., 1989. Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. Cancer Res. 49, 5111–5117.
Martinez, J., Moreno, J.J., 2000. Effect of resveratrol, a natural polyphenolic compound, on reactive oxygen species and prostaglandin production. Biochem. Pharmacol. 59, 865–870.
Matsuyama, T., Tanaka, Y., Kamimaki, I., Nagao, T., Tokimitsu, I., 2008. Catechin safely improved higher levels of fatness, blood pressure, and cholesterol in children. Obesity (Silver Spring) 16, 1338–1348.
Matthews, C.P., Colburn, N.H., Young, M.R., 2007. AP-1 a target for cancer prevention. Curr. Cancer Drug Targets 7, 317–324.
McCabe Jr., M.J., Orrenius, S., 1993. Genistein induces apoptosis in immature human thymocytes by inhibiting topoisomerase-II. Biochem. Biophys. Res. Commun. 194, 944–950.
Melnik, B.C., John, S.M., Schmitz, G., 2011. Over-stimulation of insulin/IGF-1 signaling by western diet may promote diseases of civilization: lessons learnt from laron syndrome. Nutr. Metab. (Lond.) 8, 41.
Messina, M., Nagata, C., Wu, A.H., 2006. Estimated Asian adult soy protein and isoflavone intakes. Nutr. Cancer 55, 1–12.
Metzner, J.E., Frank, T., Kunz, I., Burger, D., Riegger, C., 2009. Study on the pharmacokinetics of synthetic genistein after multiple oral intake in post-menopausal women. Arzneimittelforschung 59, 513–520.
Middleton Jr., E., Kandaswami, C., Theoharides, T.C., 2000. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. Pharmacol. Rev. 52, 673–751.
Miller, R.J., Jackson, K.G., Dadd, T., Nicol, B., Dick, J.L., Mayes, A.E., Brown, A.L., Minihane, A.M., 2012. A preliminary investigation of the impact of catechol-O-methyltransferase genotype on the absorption and metabolism of green tea catechins. Eur. J. Nutr. 51, 47–55.
Miranda, S., Gonzalez-Rodriguez, A., Revuelta-Cervantes, J., Rondinone, C.M., Valverde, A.M., 2010. Beneficial effects of PTP1B deficiency on brown adipocyte differentiation and protection against apoptosis induced by pro- and anti-inflammatory stimuli. Cell. Signal. 22, 645–659.
Montopoli, M., Ragazzi, E., Froldi, G., Caparrotta, L., 2009. Cell-cycle inhibition and apoptosis induced by curcumin and cisplatin or oxaliplatin in human ovarian carcinoma cells. Cell Prolif. 42, 195–206.
Moon, Y.J., Wang, L., DiCenzo, R., Morris, M.E., 2008. Quercetin pharmacokinetics in humans. Biopharm. Drug Dispos. 29, 205–217.
Morin, C., Zini, R., Albengres, E., Bertelli, A.A., Bertelli, A., Tillement, J.P., 2003. Evidence for resveratrol-induced preservation of brain mitochondria functions after hypoxia-reoxygenation. Drugs Exp. Clin. Res. 29, 227–233.
Mouria, M., Gukovskaya, A.S., Jung, Y., Buechler, P., Hines, O.J., Reber, H.A., Pandol, S.J., 2002. Food-derived polyphenols inhibit pancreatic cancer growth through mitochondrial cytochrome C release and apoptosis. Int. J. Cancer 98, 761–769.
Mueller, M., Beck, V., Jungbauer, A., 2011. PPARalpha activation by culinary herbs and spices. Planta Med. 77, 497–504.
Muir, C.S., Waterhouse, J.A.H., Mack, T.M., Powell, J., 1987. Cancer incidence in five continents. IARC Scientific Publications No. 88, V. International Agency for Research on Cancer, Lyon.
Muraoka, K., Shimizu, K., Sun, X., Tani, T., Izumi, R., Miwa, K., Yamamoto, K., 2002. Flavonoids exert diverse inhibitory effects on the activation of NF-kappaB. Transplant. Proc. 34, 1335–1340.
Murase, T., Misawa, K., Haramizu, S., Hase, T., 2009. Catechin-induced activation of the LKB1/AMP-activated protein kinase pathway. Biochem. Pharmacol. 78, 78–84.

Nagao, T., Meguro, S., Hase, T., Otsuka, K., Komikado, M., Tokimitsu, I., Yamamoto, T., Yamamoto, K., 2009. A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. Obesity (Silver Spring) 17, 310–317.
Nakae, J., Kitamura, T., Kitamura, Y., Biggs III, W.H., Arden, K.C., Accili, D., 2003. The forkhead transcription factor Foxo1 regulates adipocyte differentiation. Dev. Cell 4, 119–129.
Nam, S., Smith, D.M., Dou, Q.P., 2001. Ester bond-containing tea polyphenols potently inhibit proteasome activity in vitro and in vivo. J. Biol. Chem. 276, 13322–13330.
Narala, V.R., Smith, M.R., Adapala, R.K., Ranga, R., Panati, K., Moore, B.B., Leff, T., Reddy, V.D., Kondapi, A.K., Reddy, R.C., 2009. Curcumin is not a ligand for peroxisome proliferator-activated receptor-gamma. Gene Ther. Mol. Biol. 13, 20–25.
Nguyen, M.T., Favelyukis, S., Nguyen, A.K., Reichart, D., Scott, P.A., Jenn, A., Liu-Bryan, R., Glass, C.K., Neels, J.G., Olefsky, J.M., 2007. A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways. J. Biol. Chem. 282, 35279–35292.
Nieman, D.C., Williams, A.S., Shanely, R.A., Jin, F., McAnulty, S.R., Triplett, N.T., Austin, M.D., Henson, D.A., 2010. Quercetin's influence on exercise performance and muscle mitochondrial biogenesis. Med. Sci. Sports Exerc. 42, 338–345.
Nishimura, S., Manabe, I., Nagasaki, M., Eto, K., Yamashita, H., Ohsugi, M., Otsu, M., Hara, K., Ueki, K., Sugiura, S., Yoshimura, K., Kadowaki, T., Nagai, R., 2009. CD8 + effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. Nat. Med. 15, 914–920.
Nishiyama, T., Mae, T., Kishida, H., Tsukagawa, M., Mimaki, Y., Kuroda, M., Sashida, Y., Takahashi, K., Kawada, T., Nakagawa, K., Kitahara, M., 2005. Curcuminoids and sesquiterpenoids in turmeric (*Curcuma longa* L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. J. Agric. Food Chem. 53, 959–963.
Nishizuka, T., Fujita, Y., Sato, Y., Nakano, A., Kakino, A., Ohshima, S., Kanda, T., Yoshimoto, R., Sawamura, T., 2011. Procyanidins are potent inhibitors of LOX-1: a new player in the French Paradox. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 87, 104–113.
O'Dea, K., 1991. Westernisation, insulin resistance and diabetes in Australian aborigines. Med. J. Aust. 155, 258–264.
Odegaard, A.O., Koh, W.P., Butler, L.M., Duval, S., Gross, M.D., Yu, M.C., Yuan, J.M., Pereira, M.A., 2011. Dietary patterns and incident type 2 diabetes in chinese men and women: the Singapore Chinese Health Study. Diabetes Care 34, 880–885.
Oh, D.Y., Talukdar, S., Bae, E.J., Imamura, T., Morinaga, H., Fan, W., Li, P., Lu, W.J., Watkins, S.M., Olefsky, J.M., 2010. GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects. Cell 142, 687–698.
Ohara, K., Uchida, A., Nagasaka, R., Ushio, H., Ohshima, T., 2009. The effects of hydroxycinnamic acid derivatives on adiponectin secretion. Phytomedicine 16, 130–137.
Ohmura, K., Ishimori, N., Ohmura, Y., Tokuhara, S., Nozawa, A., Horii, S., Andoh, Y., Fujii, S., Iwabuchi, K., Onoe, K., Tsutsui, H., 2010. Natural killer T cells are involved in adipose tissues inflammation and glucose intolerance in diet-induced obese mice. Arterioscler. Thromb. Vasc. Biol. 30, 193–199.
Ojewole, J.A., 2006. Analgesic, antiinflammatory and hypoglycaemic effects of ethanol extract of *Zingiber officinale* (Roscoe) rhizomes (Zingiberaceae) in mice and rats. Phytother. Res. 20, 764–772.
Okura, A., Arakawa, H., Oka, H., Yoshinari, T., Monden, Y., 1988. Effect of genistein on topoisomerase activity and on the growth of [Val 12]Ha-ras-transformed NIH 3T3 cells. Biochem. Biophys. Res. Commun. 157, 183–189.
Olholm, J., Paulsen, S.K., Cullberg, K.B., Richelsen, B., Pedersen, S.B., 2010. Anti-inflammatory effect of resveratrol on adipokine expression and secretion in human adipose tissue explants. Int. J. Obes. (Lond) 34, 1546–1553.
Osaka, T., Kobayashi, A., Namba, Y., Ezaki, O., Inoue, S., Kimura, S., Lee, T.H., 1998. Temperature- and capsaicin-sensitive nerve fibers in brown adipose tissue attenuate thermogenesis in the rat. Pflugers Arch. 437, 36–42.
Ottaviani, J.I., Momma, T.Y., Heiss, C., Kwik-Uribe, C., Schroeter, H., Keen, C.L., 2011. The stereochemical configuration of flavanols influences the level and metabolism of flavanols in humans and their biological activity in vivo. Free Radic. Biol. Med. 50, 237–244.
Oyama, J., Maeda, T., Kouzuma, K., Ochiai, R., Tokimitsu, I., Higuchi, Y., Sugano, M., Makino, N., 2010. Green tea catechins improve human forearm endothelial dysfunction and have antiatherosclerotic effects in smokers. Circ. J. 74, 578–588.
Pacholec, M., Bleasdale, J.E., Chrunyk, B., Cunningham, D., Flynn, D., Garofalo, R.S., Griffith, D., Griffor, M., Loulakis, P., Pabst, B., Qiu, X., Stockman, B., Thanabal, V., Varghese, A., Ward, J., Withka, J., Ahn, K., 2010. SRT1720, SRT2183, SRT1460, and resveratrol are not direct activators of SIRT1. J. Biol. Chem. 285, 8340–8351.
Pal, D., Dasgupta, S., Kundu, R., Maitra, S., Das, G., Mukhopadhyay, S., Ray, S., Majumdar, S.S., Bhattacharya, S., 2012. Fetuin-A acts as an endogenous ligand of TLR4 to promote lipid-induced insulin resistance. Nat. Med. http://dx.doi.org/10.1038/nm.2851.
Panayiotidis, M.I., Rancourt, R.C., Pappa, A., White, C.W., 2006. Effect of cell cycle growth arrest on global DNA methylation status in human lung epithelial-like (A549) cells. In Vivo 20, 861–865.
Panunti, B., Fonseca, V., 2006. Effects of PPAR gamma agonists on cardiovascular function in obese, non-diabetic patients. Vascul. Pharmacol. 45, 29–35.
Pari, L., Murugan, P., 2007. Antihyperlipidemic effect of curcumin and tetrahydrocurcumin in experimental type 2 diabetic rats. Ren. Fail. 29, 881–889.
Park, K.K., Chun, K.S., Lee, J.M., Lee, S.S., Surh, Y.J., 1998. Inhibitory effects of [6]-gingerol, a major pungent principle of ginger, on phorbol ester-induced inflammation, epidermal ornithine decarboxylase activity and skin tumor promotion in ICR mice. Cancer Lett. 129, 139–144.
Park, J.Y., Kawada, T., Han, I.S., Kim, B.S., Goto, T., Takahashi, N., Fushiki, T., Kurata, T., Yu, R., 2004. Capsaicin inhibits the production of tumor necrosis factor alpha by LPS-stimulated murine macrophages, RAW 264.7: a PPARgamma ligand-like action as a novel mechanism. FEBS Lett. 572, 266–270.
Park, H.J., Shin, D.H., Chung, W.J., Leem, K., Yoon, S.H., Hong, M.S., Chung, J.H., Bae, J.H., Hwang, J.S., 2006. Epigallocatechin gallate reduces hypoxia-induced apoptosis in human hepatoma cells. Life Sci. 78, 2826–2832.
Park, S.Y., Jeong, K.J., Lee, J., Yoon, D.S., Choi, W.S., Kim, Y.K., Han, J.W., Kim, Y.M., Kim, B.K., Lee, H.Y., 2007. Hypoxia enhances LPA-induced HIF-1alpha and VEGF expression: their inhibition by resveratrol. Cancer Lett. 258, 63–69.
Park, H.J., Yang, J.Y., Ambati, S., Della-Fera, M.A., Hausman, D.B., Rayalam, S., Baile, C.A., 2008a. Combined effects of genistein, quercetin, and resveratrol in human and 3T3-L1 adipocytes. J. Med. Food 11, 773–783.
Park, S.S., Bae, I., Lee, Y.J., 2008b. Flavonoids-induced accumulation of hypoxia-inducible factor (HIF)-1alpha/2alpha is mediated through chelation of iron. J. Cell. Biochem. 103, 1989–1998.
Park, H.J., Della-Fera, M.A., Hausman, D.B., Rayalam, S., Ambati, S., Baile, C.A., 2009. Genistein inhibits differentiation of primary human adipocytes. J. Nutr. Biochem. 20, 140–148.
Pasarica, M., Sereda, O.R., Redman, L.M., Albarado, D.C., Hymel, D.T., Roan, L.E., Rood, J.C., Burk, D.H., Smith, S.R., 2009. Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response. Diabetes 58, 718–725.
Pedersen, S.B., Olholm, J., Paulsen, S.K., Bennetzen, M.F., Richelsen, B., 2008. Low Sirt1 expression, which is upregulated by fasting, in human adipose tissue from obese women. Int. J. Obes. (Lond) 32, 1250–1255.
Pervaiz, S., 2003. Resveratrol: from grapevines to mammalian biology. FASEB J. 17, 1975–1985.
Pfeiffer, E., Hoehle, S.I., Walch, S.G., Riess, A., Solyom, A.M., Metzler, M., 2007. Curcuminoids form reactive glucuronides in vitro. J. Agric. Food Chem. 55, 538–544.
Picard, F., Kurtev, M., Chung, N., Topark-Ngarm, A., Senawong, T., Machado, D.O., Leid, M., McBurney, M.W., Guarente, L., 2004. Sirt1 promotes fat mobilization in white adipocytes by repressing PPAR-gamma. Nature 429, 771–776.
Prabhakar, N.R., Shenoy, B.C., Simonson, M.S., Cherniack, N.S., 1995. Cell selective induction and transcriptional activation of immediate early genes by hypoxia. Brain Res. 697, 266–270.
Pungcharoenkul, K., Thongnopnua, P., 2011. Effect of different curcuminoid supplement dosages on total in vivo antioxidant capacity and cholesterol levels of healthy human subjects. Phytother. Res. 25, 1721–1726.
Qureshi, A.A., Tan, X., Reis, J.C., Badr, M.Z., Papasian, C.J., Morrison, D.C., Qureshi, N., 2011. Suppression of nitric oxide induction and pro-inflammatory cytokines by novel proteasome inhibitors in various experimental models. Lipids Health Dis. 10, 177.
Ramirez-Sanchez, I., Maya, L., Ceballos, G., Villarreal, F., 2010. (−)-Epicatechin activation of endothelial cell endothelial nitric oxide synthase, nitric oxide, and related signaling pathways. Hypertension 55, 1398–1405.
Ramudu, S.K., Korivi, M., Kesireddy, N., Lee, L.C., Cheng, I.S., Kuo, C.H., Kesireddy, S.R., 2011. Nephro-protective effects of a ginger extract on cytosolic and mitochondrial enzymes against streptozotocin (STZ)-induced diabetic complications in rats. Chin. J. Physiol. 54, 79–86.
Rausch, M.E., Weisberg, S., Vardhana, P., Tortoriello, D.V., 2008. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. Int. J. Obes. (Lond) 32, 451–463.
Ravindran, J., Prasad, S., Aggarwal, B.B., 2009. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? AAPS J. 11, 495–510.
Rayalam, S., Della-Fera, M.A., Yang, J.Y., Park, H.J., Ambati, S., Baile, C.A., 2007. Resveratrol potentiates genistein's antiadipogenic and proapoptotic effects in 3T3-L1 adipocytes. J. Nutr. 137, 2668–2673.
Rayalam, S., Yang, J.Y., Ambati, S., Della-Fera, M.A., Baile, C.A., 2008. Resveratrol induces apoptosis and inhibits adipogenesis in 3T3-L1 adipocytes. Phytother. Res. 22, 1367–1371.
Regazzetti, C., Peraldi, P., Gremeaux, T., Najem-Lendom, R., Ben Sahra, I., Cormont, M., Bost, F., Marchand-Brustel, Y., Tanti, J.F., Giorgetti-Peraldi, S., 2009. Hypoxia decreases insulin signaling pathways in adipocytes. Diabetes 58, 95–103.
Reinbach, H.C., Smeets, A., Martinussen, T., Moller, P., Westerterp-Plantenga, M.S., 2009. Effects of capsaicin, green tea and CH-19 sweet pepper on appetite and energy intake in humans in negative and positive energy balance. Clin. Nutr. 28, 260–265.
Relic, B., Zeddou, M., Desoroux, A., Beguin, Y., de Seny, D., Malaise, M.G., 2009. Genistein induces adipogenesis but inhibits leptin induction in human synovial fibroblasts. Lab. Invest. 89, 811–822.
Rios, D.R., Rodrigues, E.T., Cardoso, A.P., Montes, M.B., Franceschini, S.A., Toloi, M.R., 2008. Lack of effects of isoflavones on the lipid profile of Brazilian postmenopausal women. Nutrition 24, 1153–1158.
Rivera, L., Moron, R., Sanchez, M., Zarzuelo, A., Galisteo, M., 2008. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. Obesity (Silver Spring) 16, 2081–2087.
Rivera, L., Moron, R., Zarzuelo, A., Galisteo, M., 2009. Long-term resveratrol administration reduces metabolic disturbances and lowers blood pressure in obese Zucker rats. Biochem. Pharmacol. 77, 1053–1063.
Roberts, A.T., Martin, C.K., Liu, Z., Amen, R.J., Woltering, E.A., Rood, J.C., Caruso, M.K., Yu, Y., Xie, H., Greenway, F.L., 2007. The safety and efficacy of a dietary herbal supplement and gallic acid for weight loss. J. Med. Food 10, 184–188.
Rocha, V.Z., Folco, E.J., Sukhova, G., Shimizu, K., Gotsman, I., Vernon, A.H., Libby, P., 2008. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. Circ. Res. 103, 467–476.
Roghani, M., Baluchnejadmojarad, T., 2009. Chronic epigallocatechin-gallate improves aortic reactivity of diabetic rats: underlying mechanisms. Vascul. Pharmacol. 51, 84–89.
Roghani, M., Baluchnejadmojarad, T., 2010. Hypoglycemic and hypolipidemic effect and antioxidant activity of chronic epigallocatechin-gallate in streptozotocin-diabetic rats. Pathophysiology 17, 55–59.

Saely, C.H., Geiger, K., Drexel, H., 2010. Brown versus white adipose tissue: a mini-review. Gerontology 58, 15–23.
Sakurai, N., Mochizuki, K., Kameji, H., Shimada, M., Goda, T., 2009. (−)-Epigallocatechin gallate enhances the expression of genes related to insulin sensitivity and adipocyte differentiation in 3T3-L1 adipocytes at an early stage of differentiation. Nutrition 25, 1047–1056.
Salih, D.A., Brunet, A., 2008. FoxO transcription factors in the maintenance of cellular homeostasis during aging. Curr. Opin. Cell Biol. 20, 126–136.
Salminen, A., Hyttinen, J.M., Kaarniranta, K., 2011. AMP-activated protein kinase inhibits NF-kappaB signaling and inflammation: impact on healthspan and lifespan. J. Mol. Med. (Berl) 89, 667–676.
Sasaki, H., Sunagawa, Y., Takahashi, K., Imaizumi, A., Fukuda, H., Hashimoto, T., Wada, H., Katanasaka, Y., Kakeya, H., Fujita, M., Hasegawa, K., Morimoto, T., 2011. Innovative preparation of curcumin for improved oral bioavailability. Biol. Pharm. Bull. 34, 660–665.
Schulz, L.O., Bennett, P.H., Ravussin, E., Kidd, J.R., Kidd, K.K., Esparza, J., Valencia, M.E., 2006. Effects of traditional and western environments on prevalence of type 2 diabetes in Pima Indians in Mexico and the U.S. Diabetes Care 29, 1866–1871.
Sekiya, K., Ohtani, A., Kusano, S., 2004. Enhancement of insulin sensitivity in adipocytes by ginger. Biofactors 22, 153–156.
Senn, J.J., 2006. Toll-like receptor-2 is essential for the development of palmitate-induced insulin resistance in myotubes. J. Biol. Chem. 281, 26865–26875.
Senocak, F.S., Si, Y., Moya, C., Russell, W.K., Russell, D.H., Lee, K., Jayaraman, A., 2007. Effect of uncoupling protein-1 expression on 3T3-L1 adipocyte gene expression. FEBS Lett. 581, 5865–5871.
Seo, K.I., Choi, M.S., Jung, U.J., Kim, H.J., Yeo, J., Jeon, S.M., Lee, M.K., 2008. Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. Mol. Nutr. Food Res. 52, 995–1004.
Severson, R.K., Nomura, A.M., Grove, J.S., Stemmermann, G.N., 1989. A prospective study of demographics, diet, and prostate cancer among men of Japanese ancestry in Hawaii. Cancer Res. 49, 1857–1860.
Shan, T.Z., Ren, Y., Wu, T., Liu, C.X., Wang, Y.Z., 2009. Regulatory role of Sirt1 on the gene expression of fatty acid-binding protein 3 in cultured porcine adipocytes. J. Cell. Biochem. 107, 984–991.
Shay, N.F., Banz, W.J., 2005. Regulation of gene transcription by botanicals: novel regulatory mechanisms. Annu. Rev. Nutr. 25, 297–315.
Shi, H., Kokoeva, M.V., Inouye, K., Tzameli, I., Yin, H., Flier, J.S., 2006. TLR4 links innate immunity and fatty acid-induced insulin resistance. J. Clin. Invest. 116, 3015–3025.
Shishodia, S., Sethi, G., Aggarwal, B.B., 2005. Curcumin: getting back to the roots. Ann. N. Y. Acad. Sci. 1056, 206–217.
Si, H., Fu, Z., Babu, P.V., Zhen, W., Leroith, T., Meaney, M.P., Voelker, K.A., Jia, Z., Grange, R.W., Liu, D., 2011. Dietary epicatechin promotes survival of obese diabetic mice and *Drosophila melanogaster*. J. Nutr. 141, 1095–1100.
Simopoulos, A.P., 2008. The omega-6/omega-3 fatty acid ratio, genetic variation, and cardiovascular disease. Asia Pac. J. Clin. Nutr. 17 (Suppl. 1), 131–134.
Singh, R., Ahmed, S., Islam, N., Goldberg, V.M., Haqqi, T.M., 2002. Epigallocatechin-3-gallate inhibits interleukin-1beta-induced expression of nitric oxide synthase and production of nitric oxide in human chondrocytes: suppression of nuclear factor kappaB activation by degradation of the inhibitor of nuclear factor kappaB. Arthritis Rheum. 46, 2079–2086.
Smirin, P., Taler, D., Abitbol, G., Brutman-Barazani, T., Kerem, Z., Sampson, S.R., Rosenzweig, T., 2010. *Sarcopoterium spinosum* extract as an antidiabetic agent: in vitro and in vivo study. J. Ethnopharmacol. 129, 10–17.
Smith, A.J., Kavuru, P., Wojtas, L., Zaworotko, M.J., Shytle, R.D., 2011. Cocrystals of quercetin with improved solubility and oral bioavailability. Mol. Pharm. 8, 1867–1876.
Solinas, G., Karin, M., 2010. JNK1 and IKKbeta: molecular links between obesity and metabolic dysfunction. FASEB J. 24, 2596–2611.
Solinas, G., Vilcu, C., Neels, J.G., Bandyopadhyay, G.K., Luo, J.L., Naugler, W., Grivennikov, S., Wynshaw-Boris, A., Scadeng, M., Olefsky, J.M., Karin, M., 2007. JNK1 in hematopoietically derived cells contributes to diet-induced inflammation and insulin resistance without affecting obesity. Cell Metab. 6, 386–397.
Somparn, P., Phisalaphong, C., Nakornchai, S., Unchern, S., Morales, N.P., 2007. Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. Biol. Pharm. Bull. 30, 74–78.
Sozio, M.S., Lu, C., Zeng, Y., Liangpunsakul, S., Crabb, D.W., 2011. Activated AMPK inhibits PPAR-{alpha} and PPAR-{gamma} transcriptional activity in hepatoma cells. Am. J. Physiol. Gastrointest. Liver Physiol. 301, G739–G747.
Steffen, Y., Schewe, T., Sies, H., 2007. (−)-Epicatechin elevates nitric oxide in endothelial cells via inhibition of NADPH oxidase. Biochem. Biophys. Res. Commun. 359, 828–833.
Stewart, L.K., Soileau, J.L., Ribnicky, D., Wang, Z.Q., Raskin, I., Poulev, A., Majewski, M., Cefalu, W.T., Gettys, T.W., 2008. Quercetin transiently increases energy expenditure but persistently decreases circulating markers of inflammation in C57BL/6J mice fed a high-fat diet. Metabolism 57, S39–S46.
Stünkel, W., Campbell, R.M., 2011. Sirtuin 1 (SIRT1): the misunderstood HDAC. J. Biomol. Screen. 16, 1153–1169.
Su, H.C., Hung, L.M., Chen, J.K., 2006. Resveratrol, a red wine antioxidant, possesses an insulin-like effect in streptozotocin-induced diabetic rats. Am. J. Physiol. Endocrinol. Metab. 290, E1339–E1346.
Subauste, A.R., Burant, C.F., 2007. Role of FoxO1 in FFA-induced oxidative stress in adipocytes. Am. J. Physiol. Endocrinol. Metab. 293, E159–E164.
Surh, Y.J., 2002. Anti-tumor promoting potential of selected spice ingredients with antioxidative and anti-inflammatory activities: a short review. Food Chem. Toxicol. 40, 1091–1097.
Surh, Y.J., Park, K.K., Chun, K.S., Lee, L.J., Lee, E., Lee, S.S., 1999. Anti-tumor-promoting activities of selected pungent phenolic substances present in ginger. J. Environ. Pathol. Toxicol. Oncol. 18, 131–139.
Suzuki, J., Ogawa, M., Futamatsu, H., Kosuge, H., Sagesaka, Y.M., Isobe, M., 2007. Tea catechins improve left ventricular dysfunction, suppress myocardial inflammation and fibrosis, and alter cytokine expression in rat autoimmune myocarditis. Eur. J. Heart Fail. 9, 152–159.
Szkudelska, K., Nogowski, L., Szkudelski, T., 2000. Genistein affects lipogenesis and lipolysis in isolated rat adipocytes. J. Steroid Biochem. Mol. Biol. 75, 265–271.
Szkudelska, K., Nogowski, L., Szkudelski, T., 2008. Genistein, a plant-derived isoflavone, counteracts the antilipolytic action of insulin in isolated rat adipocytes. J. Steroid Biochem. Mol. Biol. 109, 108–114.
Szkudelska, K., Nogowski, L., Szkudelski, T., 2009. Resveratrol, a naturally occurring diphenolic compound, affects lipogenesis, lipolysis and the antilipolytic action of insulin in isolated rat adipocytes. J. Steroid Biochem. Mol. Biol. 113, 17–24.
Szkudelska, K., Nogowski, L., Szkudelski, T., 2011. Resveratrol and genistein as adenosine triphosphate-depleting agents in fat cells. Metabolism 60, 720–729.
Tewksbury, J.J., Nabhan, G.P., 2001. Seed dispersal. Directed deterrence by capsaicin in chilies. Nature 412, 403–404.
Tewksbury, J.J., Reagan, K.M., Machnicki, N.J., Carlo, T.A., Haak, D.C., Penaloza, A.L., Levey, D.J., 2008. Evolutionary ecology of pungency in wild chilies. Proc. Natl. Acad. Sci. U.S.A. 105, 11808–11811.
Thielecke, F., Rahn, G., Bohnke, J., Adams, F., Birkenfeld, A.L., Jordan, J., Boschmann, M., 2010. Epigallocatechin-3-gallate and postprandial fat oxidation in overweight/obese male volunteers: a pilot study. Eur. J. Clin. Nutr. 64, 704–713.
Thomas, R., Kim, M.H., 2005. Epigallocatechin gallate inhibits HIF-1alpha degradation in prostate cancer cells. Biochem. Biophys. Res. Commun. 334, 543–548.
Thompson, D.B., de Gregorio, M., Sommercorn, J., 1996. Insulin regulation of multiple ribonucleic acid species in human skeletal muscle in insulin-sensitive and insulin-resistant subjects. J. Clin. Endocrinol. Metab. 81, 519–523.
Timmers, S., Konings, E., Bilet, L., Houtkooper, R.H., van de, W.T., Goossens, G.H., Hoeks, J., van der, K.S., Ryu, D., Kersten, S., Moonen-Kornips, E., Hesselink, M.K., Kunz, I., Schrauwen-Hinderling, V.B., Blaak, E.E., Auwerx, J., Schrauwen, P., 2011. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. 14, 612–622.
Tsai, S.H., Lin-Shiau, S.Y., Lin, J.K., 1999. Suppression of nitric oxide synthase and the down-regulation of the activation of NFkappaB in macrophages by resveratrol. Br. J. Pharmacol. 126, 673–680.
Tuntiwechapikul, W., Taka, T., Songsomboon, C., Kaewtunjai, N., Imsumran, A., Makonkawkeyoon, L., Pompimon, W., Lee, T.R., 2010. Ginger extract inhibits human telomerase reverse transcriptase and c-Myc expression in A549 lung cancer cells. J. Med. Food 13, 1347–1354.
Ueki, S., Miyoshi, M., Shido, O., Hasegawa, J., Watanabe, T., 2008. Systemic administration of [6]-gingerol, a pungent constituent of ginger, induces hypothermia in rats via an inhibitory effect on metabolic rate. Eur. J. Pharmacol. 584, 87–92.
Vareed, S.K., Kakarala, M., Ruffin, M.T., Crowell, J.A., Normolle, D.P., Djuric, Z., Brenner, D.E., 2008. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. Cancer Epidemiol. Biomarkers Prev. 17, 1411–1417.
Varga, T., Czimmerer, Z., Nagy, L., 2011. PPARs are a unique set of fatty acid regulated transcription factors controlling both lipid metabolism and inflammation. Biochim. Biophys. Acta 1812, 1007–1022.
Venables, M.C., Hulston, C.J., Cox, H.R., Jeukendrup, A.E., 2008. Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans. Am. J. Clin. Nutr. 87, 778–784.
Vigilanza, P., Aquilano, K., Baldelli, S., Rotilio, G., Ciriolo, M.R., 2011. Modulation of intracellular glutathione affects adipogenesis in 3T3-L1 cells. J. Cell. Physiol. 226, 2016–2024.
Villa, P., Costantini, B., Suriano, R., Perri, C., Macri, F., Ricciardi, L., Panunzi, S., Lanzone, A., 2009. The differential effect of the phytoestrogen genistein on cardiovascular risk factors in postmenopausal women: relationship with the metabolic status. J. Clin. Endocrinol. Metab. 94, 552–558.
Virtanen, K.A., Lonnroth, P., Parkkola, R., Peltoniemi, P., Asola, M., Viljanen, T., Tolvanen, T., Knuuti, J., Ronnemaa, T., Huupponen, R., Nuutila, P., 2002. Glucose uptake and perfusion in subcutaneous and visceral adipose tissue during insulin stimulation in nonobese and obese humans. J. Clin. Endocrinol. Metab. 87, 3902–3910.
Vogt, P.K., 2001. Jun, the oncoprotein. Oncogene 20, 2365–2377.
Walle, T., Otake, Y., Walle, U.K., Wilson, F.A., 2000. Quercetin glucosides are completely hydrolyzed in ileostomy patients before absorption. J. Nutr. 130, 2658–2661.
Wang, B., Li, H., Yan, H., Xiao, J.G., 2005. Genistein inhibited hypoxia-inducible factor-1alpha expression induced by hypoxia and cobalt chloride in human retinal pigment epithelium cells. Methods Find. Exp. Clin. Pharmacol. 27, 179–184.
Wang, B., Wood, I.S., Trayhurn, P., 2007. Dysregulation of the expression and secretion of inflammation-related adipokines by hypoxia in human adipocytes. Pflugers Arch. 455, 479–492.
Wang, B., Wood, I.S., Trayhurn, P., 2008. Hypoxia induces leptin gene expression and secretion in human preadipocytes: differential effects of hypoxia on adipokine expression by preadipocytes. J. Endocrinol. 198, 127–134.
Wang, H., Wen, Y., Du, Y., Yan, X., Guo, H., Rycroft, J.A., Boon, N., Kovacs, E.M., Mela, D.J., 2010. Effects of catechin enriched green tea on body composition. Obesity (Silver Spring) 18, 773–779.
Wang, A., Liu, M., Liu, X., Dong, L.Q., Glickman, R.D., Slaga, T.J., Zhou, Z., Liu, F., 2011. Up-regulation of adiponectin by resveratrol: the essential roles of the Akt/FOXO1 and AMP-activated protein kinase signaling pathways and DsbA-L. J. Biol. Chem. 286, 60–66.
Wein, S., Behm, N., Petersen, R.K., Kristiansen, K., Wolffram, S., 2010. Quercetin enhances adiponectin secretion by a PPAR-gamma independent mechanism. Eur. J. Pharm. Sci. 41, 16–22.
Weisberg, S.P., Leibel, R., Tortoriello, D.V., 2008. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology 149, 3549–3558.

Weldin, J., Jack, R., Dugaw, K., Kapur, R.P., 2003. Quercetin, an over-the-counter supplement, causes neuroblastoma-like elevation of plasma homovanillic acid. Pediatr. Dev. Pathol. 6, 547–551.
Woo, H.M., Kang, J.H., Kawada, T., Yoo, H., Sung, M.K., Yu, R., 2007. Active spice-derived components can inhibit inflammatory responses of adipose tissue in obesity by suppressing inflammatory actions of macrophages and release of monocyte chemoattractant protein-1 from adipocytes. Life Sci. 80, 926–931.
Wood, I.S., Stezhka, T., Trayhurn, P., 2011. Modulation of adipokine production, glucose uptake and lactate release in human adipocytes by small changes in oxygen tension. Pflugers Arch. 462, 469–477.
Wu, H., Ghosh, S., Perrard, X.D., Feng, L., Garcia, G.E., Perrard, J.L., Sweeney, J.F., Peterson, L.E., Chan, L., Smith, C.W., Ballantyne, C.M., 2007. T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity. Circulation 115, 1029–1038.
Wu, H., Liang, X., Fang, Y., Qin, X., Zhang, Y., Liu, J., 2008. Resveratrol inhibits hypoxia-induced metastasis potential enhancement by restricting hypoxia-induced factor-1 alpha expression in colon carcinoma cells. Biomed. Pharmacother. 62, 613–621.
Yamakuchi, M., Bao, C., Ferlito, M., Lowenstein, C.J., 2008. Epigallocatechin gallate inhibits endothelial exocytosis. Biol. Chem. 389, 935–941.
Yamamoto, Y., Gaynor, R.B., 2001. Therapeutic potential of inhibition of the NF-kappaB pathway in the treatment of inflammation and cancer. J. Clin. Invest. 107, 135–142.
Yanez, M., Galan, L., Matias-Guiu, J., Vela, A., Guerrero, A., Garcia, A.G., 2011. CSF from amyotrophic lateral sclerosis patients produces glutamate independent death of rat motor brain cortical neurons: protection by resveratrol but not riluzole. Brain Res. 1423, 77–86.
Yang, J.Y., Della-Fera, M.A., Rayalam, S., Ambati, S., Hartzell, D.L., Park, H.J., Baile, C.A., 2008. Enhanced inhibition of adipogenesis and induction of apoptosis in 3T3-L1 adipocytes with combinations of resveratrol and quercetin. Life Sci. 82, 1032–1039.
Yang, H.Y., Yang, S.C., Chao, J.C., Chen, J.R., 2012. Beneficial effects of catechin-rich green tea and inulin on the body composition of overweight adults. Br. J. Nutr. 107, 749–754.
Ye, J., Gao, Z., Yin, J., He, Q., 2007. Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice. Am. J. Physiol. Endocrinol. Metab. 293, E1118–E1128.
Yon, J.M., Baek, I.J., Lee, B.J., Yun, Y.W., Nam, S.Y., 2011. Emodin and [6]-gingerol lessen hypoxia-induced embryotoxicities in cultured mouse whole embryos via upregulation of hypoxia-inducible factor 1alpha and intracellular superoxide dismutases. Reprod. Toxicol. 31, 513–518.
Yoneshiro, T., Aita, S., Kawai, Y., Iwanaga, T., Saito, M., 2012. Nonpungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans. Am. J. Clin. Nutr. 95, 845–850.
Yoon, J.S., Lee, H.J., Choi, S.H., Chang, E.J., Lee, S.Y., Lee, E.J., 2011. Quercetin inhibits IL-1beta-induced inflammation, hyaluronan production and adipogenesis in orbital fibroblasts from graves' orbitopathy. PLoS One 6, e26261.
Yoshioka, M., Imanaga, M., Ueyama, H., Yamane, M., Kubo, Y., Boivin, A., St Amand, J., Tanaka, H., Kiyonaga, A., 2004. Maximum tolerable dose of red pepper decreases fat intake independently of spicy sensation in the mouth. Br. J. Nutr. 91, 991–995.
Yu, H.N., Ma, X.L., Yang, J.G., Shi, C.C., Shen, S.R., He, G.Q., 2007. Comparison of effects of epigallocatechin-3-gallate on hypoxia injury to human umbilical vein, RF/6A, and ECV304 cells induced by Na(2)S(2)O(4). Endothelium 14, 227–231.
Yu, Y., Zick, S., Li, X., Zou, P., Wright, B., Sun, D., 2011. Examination of the pharmacokinetics of active ingredients of ginger in humans. AAPS J. 13, 417–426.
Yuan, B., Zhen, H., Jin, Y., Xu, L., Jiang, X., Sun, S., Li, C., Xu, H., 2012. Absorption and plasma disposition of genistin differ from those of genistein in healthy women. J. Agric. Food Chem. 60, 1428–1436.
Zeyda, M., Stulnig, T.M., 2007. Adipose tissue macrophages. Immunol. Lett. 112, 61–67.
Zhang, J., 2006. Resveratrol inhibits insulin responses in a SirT1-independent pathway. Biochem. J. 397, 519–527.
Zhang, Q., Tang, X., Lu, Q.Y., Zhang, Z.F., Brown, J., Le, A.D., 2005. Resveratrol inhibits hypoxia-induced accumulation of hypoxia-inducible factor-1alpha and VEGF expression in human tongue squamous cell carcinoma and hepatoma cells. Mol. Cancer Ther. 4, 1465–1474.
Zhang, Q., Tang, X., Lu, Q., Zhang, Z., Rao, J., Le, A.D., 2006. Green tea extract and (−)-epigallocatechin-3-gallate inhibit hypoxia- and serum-induced HIF-1alpha protein accumulation and VEGF expression in human cervical carcinoma and hepatoma cells. Mol. Cancer Ther. 5, 1227–1238.
Zhang, L.L., Yan, L.D., Ma, L.Q., Luo, Z.D., Cao, T.B., Zhong, J., Yan, Z.C., Wang, L.J., Zhao, Z.G., Zhu, S.J., Schrader, M., Thilo, F., Zhu, Z.M., Tepel, M., 2007. Activation of transient receptor potential vanilloid type-1 channel prevents adipogenesis and obesity. Circ. Res. 100, 1063–1070.
Zhao, J., Sun, X.B., Ye, F., Tian, W.X., 2011. Suppression of fatty acid synthase, differentiation and lipid accumulation in adipocytes by curcumin. Mol. Cell. Biochem. 351, 19–28.
Zheng, J., Ramirez, V.D., 2000. Inhibition of mitochondrial proton F0F1-ATPase/ATP synthase by polyphenolic phytochemicals. Br. J. Pharmacol. 130, 1115–1123.
Zhou, Y.D., Kim, Y.P., Li, X.C., Baerson, S.R., Agarwal, A.K., Hodges, T.W., Ferreira, D., Nagle, D.G., 2004. Hypoxia-inducible factor-1 activation by (−)-epicatechin gallate: potential adverse effects of cancer chemoprevention with high-dose green tea extracts. J. Nat. Prod. 67, 2063–2069.
Zhu, J., Yong, W., Wu, X., Yu, Y., Lv, J., Liu, C., Mao, X., Zhu, Y., Xu, K., Han, X., Liu, C., 2008. Anti-inflammatory effect of resveratrol on TNF-alpha-induced MCP-1 expression in adipocytes. Biochem. Biophys. Res. Commun. 369, 471–477.
Zhu, X., Liu, Q., Wang, M., Liang, M., Yang, X., Xu, X., Zou, H., Qiu, J., 2011. Activation of Sirt1 by resveratrol inhibits TNF-alpha induced inflammation in fibroblasts. PLoS One 6, e27081.
Zick, S.M., Djuric, Z., Ruffin, M.T., Litzinger, A.J., Normolle, D.P., Alrawi, S., Feng, M.R., Brenner, D.E., 2008. Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol and conjugate metabolites in healthy human subjects. Cancer Epidemiol. Biomarkers Prev. 17, 1930–1936.
Zick, S.M., Turgeon, D.K., Vareed, S.K., Ruffin, M.T., Litzinger, A.J., Wright, B.D., Alrawi, S., Normolle, D.P., Djuric, Z., Brenner, D.E., 2011. Phase II study of the effects of ginger root extract on eicosanoids in colon mucosa in people at normal risk for colorectal cancer. Cancer Prev. Res. (Phila.) 4, 1929–1937.
Zimmet, P., Dowse, G., Finch, C., Serjeantson, S., King, H., 1990. The epidemiology and natural history of NIDDM—lessons from the South Pacific. Diabetes Metab. Rev. 6, 91–124.
Zini, R., Morin, C., Bertelli, A., Bertelli, A.A., Tillement, J.P., 1999. Effects of resveratrol on the rat brain respiratory chain. Drugs Exp. Clin. Res. 25, 87–97.
Zoechling, A., Liebner, F., Jungbauer, A., 2011. Red wine: a source of potent ligands for peroxisome proliferator-activated receptor gamma. Food Funct. 2, 28–38.