Studies on Mechanistic Role of Natural Bioactive Compounds in the Management of Obesity An Overview

Natalia E. G. Alves[1], Samanta T. Valdés[1], Carlos M M.Silveira[1], Hércia S. D. Duarte Martino[1], Fermin I. Milagro[2], María J. Moreno-Aliaga[2] and Sônia M. R. Ribeiro[1]*

[1]*Department of Nutrition and Health, University Federal of Viçosa, 36570-000, Viçosa, MG, Brazil*

[2]*Department of Nutrition, Food Sciences, Physiology and Toxicology, University of Navarra, 31008, Pamplona, Spain*

Abstract: Obesity is recognised as a condition of low-grade chronic inflammation resulting from macrophage infiltration of adipose tissue and activation of inflammatory pathways by oxidative stress mechanisms that lead to the development of insulin resistance. Various natural bioactive compounds (NBCs) with anti-inflammatory and anti-oxidant effects may improve adipocyte dysfunction associated with metabolic syndrome. The present review focuses on the effects of phenolic compounds, n-3 long-chain polyunsaturated fatty acids (n-3 LC-PUFA) and lipoic acid (LA) on the pathophysiological mechanisms of obesity. In this review, a total of 120 studies were included, and data thus obtained reflect beneficial physiological effects of n-3 LC-PUFA, LA and different phenolic compounds, including kaempferol, luteolin, apigenin, quercetin, resveratrol, curcumin, catechins, phenolic acids, in the prevention and/or attenuation of metabolic disturbances associated with obesity. Additionally, information from clinical studies provides new insights for defining the dose-response relationship of dietary compounds, necessary time of exposure and potential side effects of these NBCs in the treatment of obesity and indicates further study is needed to verify these relationships.

Keywords: Insulin resistance, Lipoic acid, Metabolic disturbances, n-3 Long-chain polyunsaturated fatty acids, Obesity treatment, Phenolic compounds.

INTRODUCTION

Obesity is considered a major public health problem worldwide and its prevalence continues to rise uncontrollably [1]. In clinical practice, it is quite obvious that metabolic alterations in obese individuals limit the likelihood of positive response to treatment while favouring the evolution of the metabolic syndrome as well as the development of comorbidities such as diabetes and vascular complications [2]. Primary strategies for the treatment of obesity are reduction of dietary energy intake and increase of physical energy expenditure, and lifestyle changes are important for long-term success. However, a large percentage of patients to whom such treatment is recommended regain most of the weight lost during the treatment in subsequent months or years, and it is common for them to resort to expensive surgery, an invasive procedure, in an effort to achieve long-term weight loss. Thus, healthcare practitioners and the general public continue to seek more effective strategies for obesity prevention and management [3].

There is a great interest in finding adjuvant therapy for the treatment of obesity to correct or mitigate metabolic changes that increase inflammation, oxidative stress and the occurrence of comorbidities, particularly insulin resistance. Attenuation of inflammation and oxidative stress, and increased fatty acids oxidation in the adipose tissue are important points to improve the metabolism, reducing the risk of comorbidities [4-9]. Fig. (**1**), shows a representative scheme of the mechanisms related to oxidative stress and inflammation in obesity.

Natural bioactive compounds (NBCs) are substances contained in foods that provide a verifiable benefit to human health. Evidence has been shown that different NBCs modulate inflammatory genes by acting through various signalling pathways [10]. Moreover, some NBCs have the potential to improve adipocyte dysfunction associated with metabolic syndrome [11] as well as favour fatty acid oxidation and reduce lipogenesis [12]. The modulation of signalling pathways by anti-oxidant NBCs results in increased defence of several tissues against electrophilic stressors and oxidative insults; intervention in these pathways is therefore a strategy for the prevention and treatment of metabolic diseases associated with oxidative stress [13].

The aim of the present study is to review recent findings concerning the effects of three types of NBCs (phenolic compounds, n-3 LC-PUFA and lipoic acid) on obesity, including their mechanisms of action on adipocytes and on systemic levels.

*Address correspondence to this author at the Department of Nutrition and Health, University Federal of Viçosa, 36570-000, Viçosa, MG, Brazil;
Tel: 55-31-3899-2569; Fax: 55-31-3899-2541;
E-mail: nat.pedro@yahoo.com.br

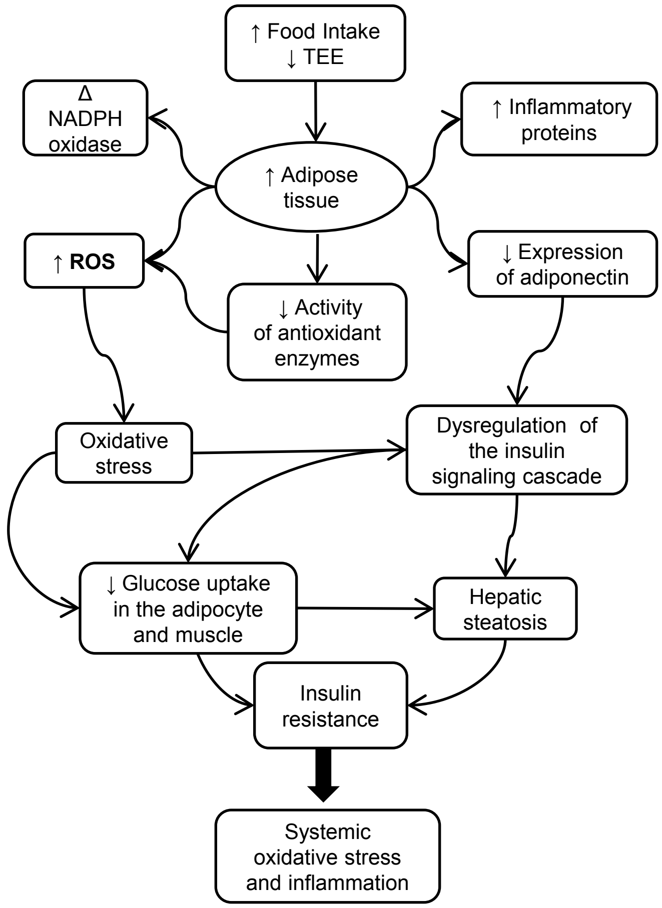

Fig. (1). Mechanisms related to oxidative stress and inflammation in obesity.
↑, increase; ↓, reduction; Δ, activation; TEE, total energy expenditure; ROS, reactive oxygen species; NADPH-oxidase, nicotinamide adenine dinucleotide phosphate-oxidase.

PHENOLIC COMPOUNDS

Polyphenols (including flavonoids and resveratrol) and phenolic acids have demonstrated anti-inflammatory and anti-adipogenic activities in several types of animal and human cells, both in *in vitro* (Table **1**) and *in vivo* models (Table **2**).

Kaempferol, Luteolin and Apigenin

Kaempferol, luteolin and apigenin (Fig. **2 a, b, c)** are flavonoids that have attracted great attention due to their ability to reduce the risks of chronic diseases through anti-inflammatory activity [14] and to alter the immune function by inhibiting enzymes that are activated in inflammatory conditions. Inactivated enzymes include the family of mitogen-activated protein kinases (MAPK - ERK, JNK and P38) that belong to the TNF-α signalling pathway, which activates nuclear factor kappa B (NF-κB) [15].

In vitro studies, described in Table **1**, have demonstrated the anti-inflammatory effects of kaempferol, luteolin and apigenin in different cell types. Macrophages, endothelial cells and 3T3-L1 adipocytes treated with kaempferol, luteolin and apigenin have shown reduced inflammatory responses. Moreover, kaempferol and luteolin induce the activation of PPAR-γ and its target genes (such as leptin, GLUT4 and adiponectin) as well as enhance insulin sensitivity in adipocytes [16-21]. Apigenin-induced activation of AMP-activated protein kinase (AMPK) that reduced the expression of adipogenic genes, thus suppressing adipogenesis in 3T3-L1 cells [22].

Kaempferol, apigenin and luteolin have the ability to block molecular mechanisms involved in triggering the inflammatory response, especially the signalling pathway of the transcription factor NF-κB, which increases the expression of genes that encode proteins involved in obesity-related inflammation. Modulation of the cyclo-oxygenase (COX) pathway by inhibition of nitric oxide production seems to be the main anti-inflammatory mechanism of action exhibited by flavonoids [23].

Benefits beyond those described above have been observed for apigenin and kaempferol. In animal studies (Table **2**), apigenin reduced food intake of C57BL/6J mice by increasing gene expression of anorexigenic neuropeptides [24]. The potential of kaempferol to increase energy expenditure should not be dismissed because this flavonoid may contribute to an increase in skeletal myocyte oxygen consumption of up to 30%, can affect regulation of metabolically important genes and activate thyroid hormones [25].

Table 1. ***In Vitro*** **Studies Showing Effects of Phenolic Compounds in the Modulation of Inflammatory Pathways and Adipogenesis**

Bioactive Compound	Cell Type	Dosage	Exposure Time	Major Effects	Reference
Kaempferol	Macrophages	25 µM	24 h	↓ STAT-1 and NF-kB	[16]
	Human endotelial cells	5 - 50µM	24 h	↓ iNOS, COX-2, NF-kB and AP-1	[17]
	Adipocytes 3T3-L1	5 -m50µM	72 h	↑ PPAR-γ, ↑ glucose uptake	[18]
Luteolin	3T3-L1 adipocytes	0.1 - 20 µM	24 h	↑ PPAR-γ, ↑ insulin sensitivity	[19]
Luteolin	Macrophages	25 µM	30 min	↓TNF-α, IL-6, iNOS and COX-2	[20]
		1, 5, 10µM	24 h	↓ TNF-α and IL-6	[21]
Apigenin	3T3-L1 adipocytes	1−50 µM	48 h	Activation of AMPK and ↓expression of adipogenic and lipolytic genes	[22]
Quercetin	3T3 – L1 adipocytes	10 – 100 µM	48 h	Activating of MAPK pathway, induction of apoptosis in mature adipocytes and modulation ERK and JNK pathways of dose-dependent manner	[30]
Quercetin	3T3-L1 adipocytes	25 µM	24 and 48 h	↓ lipid accumulation	[31]
Quercetin and Resveratrol		25 µM		↓ lipid accumulation; ↓ PPAR-γ and C/EBP α	
Quercetin and Resveratrol		100 µM		↑ release of C cytochrome from mitochondria; ↓ phosphorylation of ERK	
Quercetin	Human U937 monocytes and human primary adipocytes	3 - 30 µM	2.5 to 5 h	↓ basal expression of inflammatory genes: TNF-α, IL-6, IL-8, IL-1b, interferon-γ inducible protein-10, and cyclooxygenase-2. Prevented inflammation-mediated insulin resistance in adipocytes	[32]
Resveratrol	Human adipocytes	5- 100 µM	1- 4 d	Inhibition of preadipocyte proliferation, inhibition of adipogenic differentiation, and inhibition of lipogenesis	[38]
Resveratrol	3T3-L1 adipocytes	1 - 100 µM	3 d	↑ SIRT 1 ↓ fat accumulation	[39]
	Cells extracted from adipose tissue of male mice Sirt1$^{+/+}$ and Sirt1$^{+/-}$	50 µM		↓ fat accumulation	
		10 - 50 µM		↓ fat in retroperitoneal adipose tissue ↑ FFA and ↓ triglyceride accumulation	
Curcumin	3T3-L1 adipocytes	5-100 µM	Differenciation stage	↓ expression of FAS, down-regulates the mRNA level of PPARγ and CD36, ↓ lipid accumulation	[54]
Curcumin	3T3-L1 murine cells and in human primary preadipocytes	5-30 µM	6 d	Inhibition of mRNA levels of early adipogenic transcription factors: KLF5, C/EBPα and PPARγ	[55]
Catechin	3T3-L1 adipocytes	5-200 µM	24 h	Inhibition of cell proliferation ↓ mRNA expression of PPARγ ↓ glycerol-3-phosphate dehydrogenase activity	[61]
Catechin	3T3-L1 adipocytes	50 µM	30 min	↓ glucose uptake translocation of GLUT4 through activation of PI3K	[62]

↓, decrease; ↑, increase; STAT-1, signal transducers and activators of transcription; NF-kB, nuclear factor kappa B; iNOS, inducible nitric oxide synthase; COX-2, ciclooxigenase-2; AP-1, activator protein 1; PPAR-γ, peroxisome proliferator-activated receptors-γ; TNF-α, tumour necrosis factor-α; IL, interleukin; AMPk, AMP-activated protein kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinases; JNK, c-Jun N-terminal protein kinases; C/EBPα, CCAAT/enhancer binding protein; SIRT1, sirtuin-1; FFA, free fatty acid.

Table 1. Contd…..

Bioactive Compound	Cell Type	Dosage	Exposure Time	Major Effects	Reference
Catechin	3T3-L1 adipocytes	0.1 - 10.0 μM	Growth and differenciation phase	↓ preadipocyte proliferation with dose dependent effect, ↓ expression of C/EBPα and PPARγ	[63]
Clorogenic, o-cumaric and p-cumaric acids	3T3-L1 pre-adipocytes	100 μM	72 h	Cell cycle arrest in G1 phase	[74]
Galic acid	3T3 – L1 adipo-cytes	250 μM	72 h	Induction of apoptosis through the Fas and mitochondrial pathway; ↓ glycerol-3-phosphate dehydrogenase activity	[75]
γ -orizanol acid	Macrophages	1 mM	22 h	Supression of NF-kB activation, ↓ inflammatory response	[76]
Hydroxycinnamic acid derivatives	3T3 – L1 adipo-cytes	1 μM	72 h	Regulation of adiponectin secretion through inhibition of NF-kB activation	[77]

↓, decrease; ↑, increase; FAS, fatty acid synthase; CD36, scavenger receptor of macrophage; KLF5, Krüppel-like factor; C/EBPα, CCAAT/enhancer binding protein; PPAR-γ, peroxisome proliferator-activated receptors-γ; GLUT4, glucose transporter type-4; PI3K, Phosphoinositide 3-kinase ; NF-kB, nuclear factor kappa B.

Table 2. *In Vivo* and *Ex Vivo* Studies on the Effects of Phenolic Compounds in the Modulation of Inflammatory Pathways and Adipogenesis

Bioactive Compound	Cell Type	Dosage	Exposure Time	Major Effects	Reference
Apigenin	C57BL/6J mice	0.05% (w/w) in high-fat diet	30 d	↑anorexigen neuropeptides gene expression in neuronal cells, ↓ intake food	[24]
Kaempherol	Wistar rats	50 and 100 mg/BW/d	10 d	↓COX-2 and iNOS	[23]
Quercetin	Obese Zucker rats	10 mg/kg BW/d	10 wk	↑ adiponectin and ↓ TNF-α in visceral adipose tissue	[27]
Quercetin	C57BL/6J mice	0.8% of high-fat diet	8 wk	↓ INF-γ, IL-1α and IL-4, ↑ TEE in the 3rt week	[34]
Quercetin	Male Wistar rats	0.03% of high-fat diet	4 wk	↑ expression and secretion of adiponectin, ↑ glucose uptake ,↓ RNAm PPAR-γ and ↓ 8-iso-PGF2α	[35]
Resveratrol	C57BL/6NI mice	22.4 mg/ kg BW/d	1 year	↑ insulin sensitivity, ↑ AMPK and UCP1, ↓ IGF-1, ↑ PGC-1α	[44]
Resveratrol	Primates (Microcebus murinus) (n=6)	200 mg/kg BW/d	4 wk	↓ 13% caloric intake, ↑ RMR from 12.7 to 29%, ↑ GLP-1	[45]
Resveratrol	Male C57BL/6J mice	400 mg/ kg high-fat diet	10 wk	↓ food intake, ↓visceral fat-pad weights, ↓adipocyte size in epididymal adipose tissue, ↓ serum lipids and improve markers of inflammation and insulin resistance	[46]
Resveratrol	Male Wistar rats fed high-fat diet	30 mg/kg BW/d	6 wk	↓ 20% fat body, ↓triglycerides, ↑glycemic control	[47]
Resveratrol	Healthy obese men (n=11)	150 mg/kg BW/d	30 d	In muscle: activation AMPK, ↑SIRT1 and PGC-1α protein levels, ↑citrate synthase intramyocellular lipid content. ↓intrahepatic lipid content, serum glucose, triglycerides, alanine-aminotransferase, and inflammation markers and HOMA index improvement	[51]

Table 2. Contd…..

Bioactive Compound	Cell Type	Dosage	Exposure Time	Major Effects	Reference
Curcumin	C57/BL mice	500 mg/kg high-fat diet	12 wk	↓serum cholesterol and expression of PPAR- γ and CCAAT/enhancer binding protein alpha; suppression of angiogenesis in adipose tissue ↓ expression of vascular endothelial growth factor (VEGF) and its receptor VEGFR-2, ↓Body weight gain, adiposity, and microvessel density in adipose tissue	[56]
Catechin	Trial: 98 men and 99 women heatlhy (Japan) (IMC: 22.5 a 30 kg/m²)	Extract of green tea (665.9 mg/d)	12 wk	↓ body weight and BMI, ↓ waist perimeter and waist-hip ratio, ↓ total cholesterol and LDL-c	[64]
Catechin	Trial: healthy men (n=38)	Tea (690 mg catechin/d)	12 wk	↓ body weight and BMI, ↓ waist perimeter and waist-hip ratio, ↓ total cholesterol and LDL-c	[65]
Catechin	Trial: men and women (Japan) with visceral obesity) (n=270)	Green tea (583 mg catechin/d)	12 wk	↓ body weight and BMI , ↓waist perimeter and waist-hip ratio, ↓ LDL-c and blood pressure	[66]
Catechin	Cross-sectional: 569 men, 641 women (Taiwan)	435 mL green tea/d	≥ 10 years	Improved 19.6% glycemic control, ↓ 2.1% waist-hip ratio	[67]
γ-orizanol acid	C57BL/6J mice	14.5 μg/ml	30, 54 and 102 h after exposition	Prevention of stress-induced hypoadiponectinemia and improvement o metabolic syndrome aggravated by chronic stress	[78]
Orizanol acid	C57BL6J mice	0.025 mM in 0,5 mL of beef tallow or corn oil	96 h after intake	Reversal of hipoadiponectinemia induced by ingestion of animal fat	[79]
O-cumáric acid	Wistar rats	100 mg/Kg diet	8 wk	↓ body weight and epididimal and peritoneal adipose tissue ↓ serum lipidis, ↓ insulin and leptin, ↓ oxidative stress	[80]
Orizanol acid	C57BL/6J mice	0.5% oryzanol Or 0.5% ferulic acid in high-fat diet	7 wk	↓blood glucose level, ↓ activities of enzymes glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, ↑ glycogen and insulin concentrations, ↑glucokinase activity, ↓ body weight	[81]
Clorogenic acid	ICR mice	0.2 g/kg de diet	8 wk	Regulation of lipid metabolism in adipocyte through enzymatic inhibition of three enzymes: fatty acid synthase, 3-hydroxy-3-methylglutaryl CoA reductase and acyl-CoA cholesterol acyltransferase	[82]
Galic acid	Male Wistar rats	50 and 100 mg/kg	10 wk	↓ dyslipidemia, hepatic steatosis and oxidative stress	[83]
Clorogenic acid	Trial: healthy individuals (IMC 27.5-32) (n= 12)	11 g coffee enriched with clorogenic acid (90 – 100 mg) / d	12 wk	↓ body weight and fat percentage	[85]

↓, decrease; ↑, increase; COX-2, ciclo-oxygenase2; iNOS, inducible nitric oxide synthase; TNF- α , tumor necrosis factor- α; INF-γ, interferon-gamma; IL, interleukin; TEE, total energy expenditure; PPAR-γ, peroxisome proliferator-activated receptors-γ; 8-isso-PGF2α, prostaglandin2;AMPK, AMP-activated protein kinase; UCP1, mitochondrial uncoupling proteins; IGF-1, insulin-like growth factor 1; PGC-1 α , peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; RMR, resting metabolic rate; Sirt1, sirtuin-1; GLP-1, glucagon-like peptide-1; SIRT1, sirtuin-1; HOMA, homeostasis model assessment; VEGF, vascular endothelial growth factor; VEGFR-2, vascular endothelial growth factor receptor 2
↓, decrease; ↑, increase; BMI, body mass index, LDL-c, low-density-lipoprotein cholesterol

It is noteworthy that most studies on these compounds have been performed In vitro with the aim to clarify mechanisms of action; they have been focused on elucidating implications for inflammation. Human intervention studies are needed to confirm the health benefits and to establish the dose-response relationship for kaempferol, apigenin and luteolin in obesity treatment.

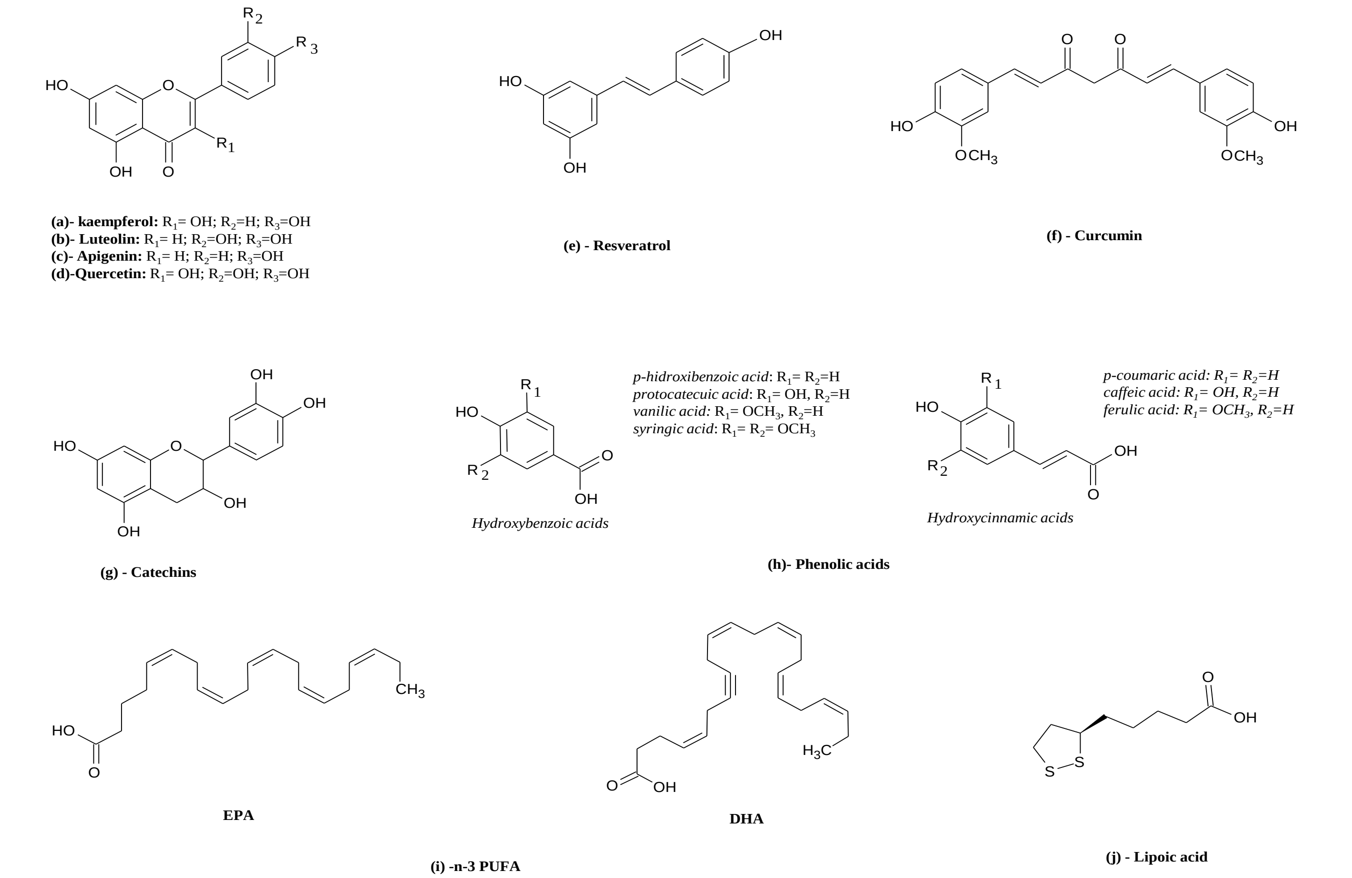

Fig. (2). Chemical structures of bioactive compounds. EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

Quercetin

Quercetin (Fig. **2d**) is a flavonoid that has been noted for beneficial effects on human health associated with its anti-oxidant [26] and anti-inflammatory [27] properties. It may also modulate LDL-cholesterol levels [28] and blood pressure [29].

The anti-adipogenic effects of quercetin have been demonstrated in 3T3-L1 and human adipocytes, whereas its anti-inflammatory effects have been revealed in macrophages (Table **1**). The main anti-adipogenic mechanism is the induction of apoptosis through modulation of extra-cellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) pathways [30]. When combined with resveratrol, quercetin has decreased lipid accumulation and inhibited PPAR-γ and C/EBP transcription factors. Both bioactive compounds, combined at concentrations of 100 µM, resulted in increased release of cytochrome C from mitochondria to the cytosol and decreased ERK phosphorylation [31]. In human cells, quercetin prevented inflammation and insulin resistance in adipocytes exposed to macrophage-conditioned media [32]. Indeed, there is evidence that quercetin is at least as effective as resveratrol at attenuating TNF-α-mediated inflammation and insulin resistance in primary human adipocytes [33].

The anti-inflammatory effects of quercetin in adipose tissue have been confirmed in animal studies, as shown in Table **2**. Its effects include evident improvement in the degree of inflammation, increased plasma and mRNA levels of adiponectin, and decreased TNF-α production in visceral adipose tissue [27, 34, 35]. Thus, in mice fed a high fat diet (45%), a supplementation with 0.8% quercetin had no effect on body weight or body composition, but induced a reduction in the levels of inflammatory markers (IFN-γ, IL-1 α and IL-4) [34].

Beneficial effects of quercetin on energy metabolism and glucose uptake have also been observed. A transient increase on energy expenditure was observed during the third week of quercetin supplementation in mice fed with high-fat diet followed by a reduction in circulating quercetin between weeks 3 and 8, suggesting a metabolic adaptation to the early effects of quercetin on energy expenditure [34].

In high-fat-fed *Wistar* rats, a supplementation containing 0.03% quercetin reduced fasting glucose levels, increased plasma and mRNA levels of adiponectin, decreased oxidative stress in plasma (measured as 8-iso-PGF2a), and decreased PPAR-γ mRNA levels in adipose tissue [35]. These authors also observed that quercetin stimulated the secretion of adiponectin by mechanisms independent of PPAR-γ.

In summary, the anti-inflammatory, anti-oxidant and pro-apoptotic effects of quercetin may prove to be useful in the treatment of obesity. The first and the second mechanisms are currently considered the primary instigators of patho-physiological alterations related to the onset of metabolic syndrome. However, further human intervention studies are needed to confirm the efficacy of quercetin in reducing body fat and improving pathophysiological changes. In addition, it is necessary to establish recommendation for adequate dosage and exposure times.

Resveratrol

Resveratrol (Fig. **2e**) is a phenolic compound that exhibits anti-inflammatory and cardioprotective effects that are partially attributed to its high anti-oxidant activity [36, 37]. Several *in vitro* and *in vivo* studies have demonstrated the effects of resveratrol in the regulation of adipogenic mechanisms and inflammatory processes.

The results of the *in vitro* studies, as shown in Table **1**, indicate that resveratrol exerts the following beneficial effects on obesity management: a decrease in lipid synthesis in adipocytes by PPAR-γ supression, an increase in lipolysis, and a reduction in lipid accumulation in maturing preadipocytes [38, 39], through the inhibition of lipogenesis and differentiation of 3T3-L1 adipocytes *via* activation of AMPK in a dose-dependent manner [40], and in the inhibition of adipogenesis by means of GSH up-regulation [41].

Through the mechanisms described above, resveratrol may decrease the expression and secretion of proinflammatory adipokines such as IL-6, TNF-α and PAI-1 [42], increase the expression and secretion of adiponectin [43], and improve mitochondrial oxidative function by increasing sirtuin activity [38], mitochondrial biogenesis and fatty acid oxidation [39].

The results of *in vivo* studies in rats (Table **2**) have shown that resveratrol induces changes associated with longevity including increased insulin sensitivity, reduced levels of insulin-like growth factor (IGF-1), increased AMPK and quantity of mitochondria, increased activity of PGC-1α and improved motor function of animals [44]. In primates, resveratrol reduced the body weight gain by increasing satiety and resting metabolic rate [45]. In mice fed with a high-fat diet, resveratrol decreased food intake and down-regulated adipogenic and inflammatory processes [46]. Intra-peritoneal administration of resveratrol in mice suppressed food intake by 20.0% and 17.2% for 24 and 48 h, respectively. The inhibition of food intake was mediated by a down-regulation of neuropeptide Y and agouti-related protein, two neuropeptides involved in satiety [47].

Still, the ability of resveratrol to induce a reduction in food intake has not been universally observed [45, 46, 48, 49]. This difference could be attributed to the dose and period of supplementation. However, even in short-term studies, and before weight reduction, resveratrol improved the metabolic state inherent to obesity [50]. In overweight subjects, resveratrol also displayed several beneficial effects on muscle metabolism by reducing inflammatory markers and insulin resistance [51].

A consensus exists regarding the beneficial effects of resveratrol on adipogenesis mitigation. However, its benefits on obesity treatment should be further studied, focusing special attention on the establishment of safe doses and the adequate intake of this compound to attenuate inflammation and metabolic alterations. Data suggest that the potential therapeutic application of resveratrol as an adjunct in the obesity treatment should be exploited because, in addition to direct effects on adipocytes, its supposed appetite-reducing effect is very attractive. In clinical practice, unregulated appetite is a major constraint to the maintenance of body weight in obese individuals.

Curcumin

Curcumin (Fig. **2f**) is a polyphenol extracted from the rhizomes of turmeric (*Curcuma longa* L) [52]. It is known for its beneficial health effects attributed to anti-inflammatory, anti-oxidant and hypolipidemic properties [53].

Different *in vitro* assays (Table **1**) have demonstrated that curcumin inhibits adipocyte differentiation [54, 55] and decreases lipid accumulation by reducing the expression of fatty acid synthase (FAS), as well as by down-regulating the PPAR-γ and CD36 mRNA levels during adipocyte differentiation [54]. In C57/BL mice (Table **2**), curcumin reduced body weight gain and adiposity, decreased serum cholesterol and caused suppression of angiogenesis in adipose tissue [56].

In addition to its direct action on the adipocyte, evidence has been shown that curcumin attenuates obesity-associated metabolic changes in the liver by blocking leptin signalling through reducing leptin receptor phosphorylation and inducing an increase in adiponectin secretion, which is important for improving obesity-associated inflammation [57]. These results provide novel insights into the therapeutic mechanisms of curcumin to improve hepatic metabolism and attenuate changes associated with non-alcoholic steatohepatitis [58]. These effects have great therapeutic value due to the common occurrence of hepatic dysfunction in the obese.

A recent review concluded that curcumin may interact with proteins in adipocytes, down-regulating inflammatory adipocytokines, resistin and leptin, and up-regulating adiponectin. The interactions of curcumin with several signal transduction pathways should reverse insulin resistance, hyperglycemia, hyperlipidemia, and other inflammatory symptoms associated with obesity and metabolic diseases [59]. Nevertheless, studies in humans are needed to explore the effects of curcumin in the treatment and control of metabolic abnormalities linked to obesity because knowledge at this level is still scarce.

Catechins

Catechins (Fig. **2g**), such as (−)-epicatechin, 3-O-galloyl-(−)-epicatechin, (−)-epigallocatechin and epigallocatechin 3-gallate (GEGC), are polyphenols present in high concentrations in tea [60]. Green tea and catechins have been demonstrated in cell culture (Table **1**), human trials and cross-sectional studies (Table **2**) that may reduce adipocyte differentiation and proliferation, lipogenesis [61-63], fat mass, body weight, oxidised LDL-c and blood pressure, and can improve glycemic control [64-67]. GEGC has been widely investigated for its possible body fat-reducing effects.

Evidences have shown that the anti-adipogenic effects of catechins are mediated by several mechanisms including the inhibition of cell proliferation, a decrease in PPAR-γ and C/EBP-α expression, an increase in glucose uptake [61-63], and the induction of thermogenesis *via* sympathetic nervous system through inhibition of the enzyme catechol-O-methyltransferase as well as noradrenaline enhancement [68]. Moreover, reduced body fat accumulation may also be explained by a decrease in the digestibility of the diet [69, 70], higher faecal energy loss, increased post-prandial fat oxidation and a reduction in dietary lipid incorporation into adipose tissue, liver and skeletal muscle [70].

These results have suggested the promising therapeutic potential of catechins in obesity management. Recent studies emphasise many benefits of beverages rich in catechins, including the improvement of body composition and lower abdominal adiposity in moderately overweight subjects [71] and the attenuation of oxidative stress [72]. In diabetic subjects, catechin-rich beverages have also contributed to reducing body weight, increasing adiponectin secretion and recovering insulin-secretory ability [73].

Despite evidence of health benefits from bioactive compounds in tea, many doubts still remain regarding its potential in the treatment of obesity. The present review has verified that many different types of tea and different dose ranges reflecting varying levels of catechin ingestion were employed in studies to date. Moreover, the method of preparation and geographic origin of tea plants can influence catechin content and, therefore, the bioactivity of each tea and its extracts. All of these factors should be taken into account in the use of green tea as an adjunct in obesity management.

Phenolic acids

Phenolic acids (Fig. **2h)** constitute a broad class of compounds that are divided into two main groups, hydroxycinnamic acids (caffeic, ferulic, coumaric and synaptic acids) and hydroxybenzoic acids (gallic, p-hydroxybenzoic, protocatechuic, vanillic and syringic acids) [60]. Among the biological activities of phenolic acids, their anti-oxidant and anti-inflammatory properties have attracted great attention. Additionally, adipose tissue is a target of action for phenolic acids as shown in the studies described in Tables **1** and **2**.

In vitro studies (Table **1**) using adipocytes and macrophages have revealed some of the mechanisms of action of phenolic compounds and their derivatives, which may explain the results observed in *in vivo* studies, such as the inhibition of adipocyte proliferation, the inhibition of enzymes involved in carbohydrate metabolism and lipid pathways, the attenuation of inflammation and the consequent improvement of adipocyte metabolism [74-77].

In vivo studies (Table **2**) have revealed a reduction in inflammatory markers and oxidative stress, a decrease in body weight and improvements in carbohydrate and lipid metabolism by phenolic acid activity [78-85]. For example, hydroxycinnamic acids and their derivatives may regulate adiponectin secretion by inhibiting NF-kB and leukotriene formation [78], but they may also have anti-oxidant and anti-glycation properties [86]. Ferulic acid and its derivative, gamma-oryzanol, reduced the risk of high-fat diet-induced hyperglycemia *via* regulation of insulin secretion and hepatic glucose-regulating enzyme activities [81]. A recent review has shown that ferulic acid derivatives may mediate anti-inflammatory effects by down-regulating the pro-inflammatory transcription factor NF-κB, which in turn can reduce the expression of inflammatory enzymes, such as COX-2 and iNOS, and pro-inflammatory cytokines, such as IL-1β, IL-6 and TNF-α. Moreover, these bioactive compounds could up-regulate blood adiponectin levels *via* indirect activation of PPAR-γ through NF-κB inhibition [87].

In summary, the primary beneficial effects attributed to phenolic acids are due to their anti-oxidant activity, regulation of adiponectin secretion, suppression of inflammatory responses, inhibition of the cell cycle and induction of adipocyte apoptosis. However, most studies have been performed *in vitro* or in animals. Human intervention studies are needed to investigate physiological effects and dose-response, as well the synergistic action between several types of phenolic acids on metabolic alterations related to human obesity. It seems that derivatives of phenolic acids in the form of esters have greater pharmacological potential in adipose tissue [87, 88], and this must be further investigated.

n-3 Long-chain Polyunsaturated Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Fig. **2i**) are polyunsaturated fatty acids (n-3) that have been highly investigated because of their functional properties in adipose tissue.

In vitro studies (Table **3**) have shown that both fatty acids inhibit adipocyte differentiation, increase cell apoptosis, and up-regulate the expression of PPAR-γ, as well as proteins that enhance glucose uptake and improve insulin resistance [89-92]. Moreover, EPA has been shown to decrease the TNF-α-induced activation of lipolysis and NF-kB and ERK1/2 signalling pathways in 3T3-L1 adipocytes [93]. The beneficial metabolic effects of DHA and EPA have also been related to their ability to promote AMPK activation and to regulate adipokine secretion [94-96].

In vivo studies (Table **4**) have demonstrated that EPA improves insulin resistance and hypolipidemia in animals fed a high-fat diet, reduces adipose tissue inflammation and visceral adiposity, increases adipocyte apoptosis and serum adiponectin, and up-regulates mitochondrial biogenesis, which may induce β-oxidation in white fat [97-101]. The reduction in retroperitoneal adipose tissue has aroused great interest since an increase in fat deposits in this area is highly associated with metabolic abnormalities related to obesity.

At concentrations commonly consumed in the diet, EPA and DHA have shown little effect on body composition in animals [102, 103]. However, the supplementation of fatty acids at a higher dosage, when associated with diets restrictive in energy, seems to potentiate weight loss [104, 105].

Despite the evidence described above, human trials have not always demonstrate the benefits of EPA and DHA supplementation in the treatment of obesity [106]. The dosage of fatty acid supplementation that could result in bioactivity necessary for obesity treatment is difficult to establish because these compounds are already present in the diet and have been combined in different proportions in each study. Distinct combinations and dietary influence can induce the anti-inflammatory effects of these fatty acids on the body.

Table 3. *In Vitro* Studies Showing Effects of n-3 Long-chain Polyunsaturated Fatty Acids and Lipoic Acid in the Modulation of Inflammatory Pathways and Adipogenesis

Bioactive Compound	Cell Type	Dosage	Exposure Time	Major Effects	Reference
DHA	3T3-L1 adipocytes	25 - 200 μM	10 d	↓ glycerol-3-phosphate dehydrogenase, ↓ cell size and lipid accumulation of dose-dependent manner and ↑ apoptosis and ↑ lipolysis	[89]
DHA	3T3-L1 adipocytes	125 μM	24 h	↑ secretion and mRNA of adiponectin	[90]
EPA	3T3-L1 adipocytes	200 μM	24 h	↑ secretion and expression of apelin	[91]
EPA	Human adipocytes	100 μM	48 h	↑ adiponectin secretion	[92]
EPA	Primary rat and 3T3-L1 adipocytes	100 and 200 μM	24 and 96 h	↓ IL-6-induced lipolysis, modulation of anti-inflammatory mechanisms involving protein phosphorylation	[93, 96]
EPA	Primary cultured rat and 3T3-L1 adipocytes	200 μM	24 and 96 h	Modulation (in visceral fat) of gene expression and protein secretion appointed as involved in insulin resistance	[94]
Alpha-lipoic acid	3T3-L1 adipocytes	0.1 - 10 μM	24 h	↑ mitochondrial mass, ↑ expression of mitochondrial DNA, ↑ mitochondrial complexes, ↑ oxygen consumption and ↑ fatty acid oxidation	[105]
Alpha-lipoic acid	3T3-L1 adipocytes	100, 250 and 500 μM	1, 2, 3, 6 d	Modulation of adipocyte differentiation by regulation pro-adipogenic transcription factors *via* mitogen-activated protein kinase pathways. Biphasic mode of LA action on mRNA levels of the adipogenic transcription factors	[108]
Alpha-lipoic acid	3T3-L1 adipocytes	250 mM	1 h	↑ phosphorylation of Sp1 and inhibition Sp1, transcriptional activity, inhibition of leptin	[109]
Alpha-lipoic acid	3T3-L1 adipocytes	250 μM	24 h	↑ apelin secretion	[110]
Alpha-lipoic acid	T cells	50 and 100 μg/ml	5 min	↓ IL-6 levels, ↓ IL-17 ,↓ inflammation *via* cAMP and protein kinase A signaling	[111]

↓, decrease; ↑, increase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin; LA; alpha-lipoic acid; Sp1, SV40 promoter-1; cAMP, cyclic adenosine monophosphate.

Lipoic Acid

Lipoic acid (LA, Fig. **2j**) is an organo-sulfur compound derived from caprylic acid that acts as a co-factor of mitochondrial enzymes. It is synthesised in the human body, but is also widely distributed in foods and has attracted much interest because of its anti-oxidant effects and therapeutic potential [107].

In vitro studies (Table **3**) have demonstrated the effect of LA in modulating adipogenesis [108] and the production of adipokines, such as leptin, adiponectin and apelin. These alterations improve mitochondrial function by stimulating organelle biogenesis, increasing fatty acid oxidation and reducing inflammation [109-111].

Animal studies (Table **4**) have demonstrated that LA can be beneficial for obesity management through different mechanisms including reduction of inflammation *via* cAMP and protein kinase A signalling, prevention of high-fat diet-induced weight gain, slight increase in apelin expression, and decrease in intestinal sugar uptake and insulin resistance [110, 112, 113].

Human trials appear to confirm the beneficial effects of LA in obesity (Table **2**). In obese subjects, supplementation with LA resulted in greater reduction in body weight, abdominal circumference, and blood pressure [114, 115]. However, short-term LA supplementation did not prevent the lipid-induced dysregulation of glucose homeostasis in obese and overweight non-diabetic men [116].

These data reinforce the importance of better exploring the therapeutic value of LA in the treatment of obesity. Bimodal action depending on the LA concentration observed *in vitro*, needs to be investigated *in vivo.*

DISCUSSION

As mentioned previously, in regards to obesity the dysfunction of the adipocyte leads to systemic metabolic consequences that are triggered especially through pro-oxidant and pro-inflammatory mechanisms (Fig. **1**). The present review confirms that different phenolic compounds and fatty acids share a common anti-oxidant effect in adipose tissue. This conclusion leads one to question the usefulness of oxidative stress reduction in adipose tissue as an approach to obesity management. Data appear to affirm this approach. Oxidative stress is considered one of the mechanisms responsible for the impairment of adipocyte function in obesity. It leads to the modulation of gene expression regulated by redox

Table 4. *In Vivo* and *Ex-Vivo* Studies Showing Effects of n-3 Long-chain Polyunsaturated Fatty Acids and Lipoic Acid in the Modulation of Inflammatory Pathways and Adipogenesis

Bioactive Compound	Cell Type	Dosage	Exposure Time	Major Effects	Reference
EPA	C57BL/6J mice	36 g/kg of high-fat diet	11 wk	↓ adipose inflammation and lipogenesis, ↑markers of fatty acid oxidation, ↓ saturated fat-induced insulin resistance	[97]
EPA and DHA	C57BL/6J mice	6% EPA plus 51% DHA diet	4wk	↑ genes of mitochondrial proteins, ↑ expression of CTP-1 gene ↑ fatty acid oxidation in epididymal fat	[98]
EPA	Wistar rats	1 g/kg/d	5wk	↓ weigh body gain, ↓intake food, ↑ production of leptin, ↓ PPARγ, ↑ apoptosis; ↓ TNF-a, ↑ adiponectin	[99]
EPA	Wistar rats: standard and high-fat diets	1 g/kg/d	35 d	↓ retroperitoneal fat, ↓ epididymal fat, ↓ IL-6 mRNA	[100]
EPA	Wistar rats: standard and high-fat diets	1 g/kg/d	5 wk	Down-regulation of genes involved in fatty acid synthesis: acetyl CoA carboxylase in muscle and liver fatty acid synthase	[101]
Alpha-lipoic acid	Wistar rats: standard and high-fat diets	0.25 g LA/100 g of diet	8 wk	↑ apelin mRNA, ↓ intake food, ↓ fat mass, prevented obesity	[110]
Alpha-lipoic acid	Wistar rats fed high-fat diet	0.25 g LA/100 g of diet	8 wk	Prevents body weight gain, reduces intestinal sugar transport	[112]
Alpha-lipoic acid	Wistar rats fed standard and high-fat diets	0.25 g LA/100 g of diet	8 wk	↑adiponectin/total WAT ratio, ↑AMPK, negative correlation between HOMA index and serum adiponectin/total WAT ratio	[113]
Alpha-lipoic acid	Human trial	1200 mg LA	6 h after intake	Anti-inflammatory effects of LA are mediated in part by the cAMP/PKA signaling cascade	[114]
Alpha-lipoic acid	Human trial: 1127 obese, and pre-obese individuals	800 mg/d	120 d	Higher reduction of body weight, abdominal circumference and blood pressure	[115]
Alpha-lipoic acid	Human trial: 360 obese individuals	1200 or 1800 mg/d	20 wk	Significantly greater weight loss for 1800 mg/d	[116]

↓, decrease; ↑, increase; C; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; CTP-1, mitochondrial citrate transport protein; PPAR-γ, peroxisome proliferator-activated receptors-γ; TNF-α, tumour necrosis factor-α; IL- interleukin; WAT, white adipose tissue; HOMA; homeostasis model assessment; LA, lipoic acid; cAMP, cyclic adenosine monophosphate.

mechanisms, especially those involved in inflammation and insulin signalling [117]. In fact, in obesity, the production of ROS is increased in adipose tissue [9] and enzymatic antioxidant mechanisms are inhibited [118].

Although the expression of several proteins can be modulated by NBCs, the effect of prolonged exposure on the profile of expressed genes remains unknown. Doubts remain as to whether the down- and up-regulatory mechanisms are permanent or transient; thus, recommendation cannot be made as to the best method of NBC exposure for obesity treatment: chronic or pulse exposures and dosages. All of this needs to be clarified in future studies.

This review (Tables **1, 2, 3** and **4**) reveals that in *in vitro* assays, the exposure time of the adipocytes to the action of bioactive compounds varied between 5 minutes and 10 days. Similarly, in human and animal studies, the period of supplementation ranged from 30 hours to 120 days. Long-term supplementation studies remain unavailable.

Another issue that merits discussion is the concentration of compounds used in these studies. Most NBCs in this review are contained in foods at very low concentrations. Considering the numerous factors that affect their bioavailability in the human body, it is assumed that dietary intake of these NBCs through foods would not result in concentrations at the adipocyte comparable to those used in experimentation. Thus, many *in vitro* assays may be demonstrative of the pharmacological effects of these bioactive compounds and not the physiologically attainable levels. Moreover, little is known about the serum levels of such bioactive compounds in the general population and the concentrations reached in the target tissues.

All of these considerations suggest that to obtain the effects of these bioactive compounds as observed in the studies reviewed here, supplementation is the most adequate strategy. For example, to increase the bioavailability of NBCs, nanoparticles of proteic or lipidic nature could be used [119]. Consequently, it is recommended that future studies test lower concentrations of these bioactive compounds to clarify potential nano-bioactivity in the modulation of gene expression. Another approach is the study of synergistic effects *via* the combination of these NBCs.

The potential of NBCs to attenuate inflammation, prevent oxidative stress, and improve metabolic activity of the adipocyte is an exciting approach to the treatment of obesity. Several mechanisms of great pathophysiological significance can be modulated by these compounds, especially oxidative stress, inflammation and adipocyte differentiation (Fig. **3**).

The collected evidence suggests that the NBCs discussed in this review exhibit the ability to reduce inflammation and improve insulin resistance in adipose tissue through several mechanisms, such as increased lipid oxidation and stimulation of mitochondrial biogenesis in adipose tissue as well as lipotropic effects in the liver. The latter effect should not be neglected, although this aspect is beyond the scope of this work. It is known that the metabolic changes that occur in the liver as a result of obesity are important mechanisms that underlie development of metabolic syndrome and insulin resistance [120].

The traditional and simplistic idea that correction for the imbalance between caloric intake and energy expenditure is adequate treatment for obesity must be revolutionized. There is convincing scientific evidence that adipose tissue metabolism is modulated by NBCs. This modulation results in beneficial systemic effects by minimizing lipotoxicity in other tissues reducing the risk of comorbidities associated with obesity. However, it is noteworthy that the effects of NBCs should only be considered as adjuvants in the treatment of obesity. Gene modulation by NBCs can help to optimise therapy through intervention in the metabolic changes that hinder the success of treatment, support the obese state, and increase the risk of comorbidities. However, the restoration of energy balance by decreasing caloric intake and/or increasing energy expenditure will always be the main objective in obesity treatment, something for which nutritional education remains crucial.

CONCLUSION

The aforementioned food compounds may act on transcriptional gene regulation, metabolic processes and hormone levels by diverse mechanisms. Their primary activities involve reducing the inflammatory response and oxidative stress, decreasing insulin resistance and stimulating mitochondrial biogenesis and lipolysis. However, information from clinical studies to define the dose-response relationship,

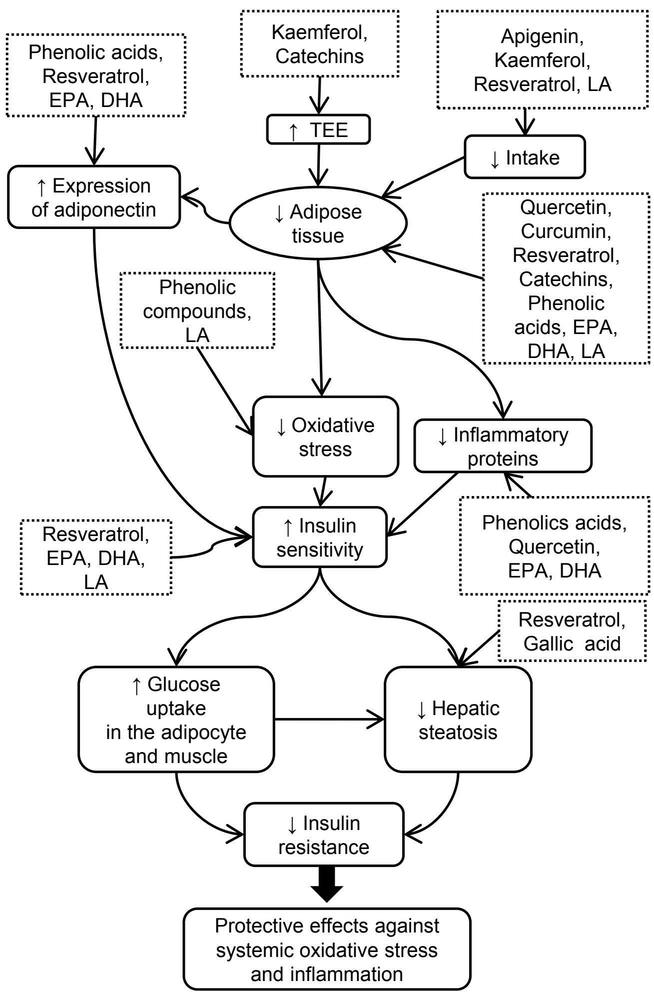

Fig. (3). Targets for action of phenolic compounds, EPA, DHA and lipoic acid to improve pathophysiological conditions in obesity. ↓, reduction;↑, increase; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid, LA, lipoic acid; TEE, total energy expenditure.

necessary time of exposure and potential side effects of these NBCs in the treatment of obesity is lacking. In conclusion, despite evidence that phenolic compounds, EPA, DHA, and LA have the potential to modulate the metabolic and secretory functions of adipose tissue, which could lead to clinically significant systemic effects in the management of obesity, clinical studies are required to establish their effective and safe use.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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