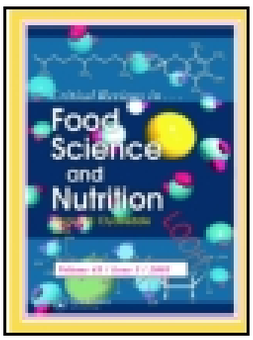

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Phenolic compounds as natural and multifunctional anti-obesity agents: A review

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ABSTRACT

Prevalence of obesity worldwide has reached pandemic proportions. Despite the increasing evidence in the implication of phenolic compounds in obesity management, the real effect is not completely understood. The available *in vitro* and *in vivo* studies have demonstrated the implication of phenolic compounds in: lowering food intake, decreasing lipogenesis, increasing lipolysis, stimulating fatty acids β-oxidation, inhibiting adipocyte differentiation and growth, attenuating inflammatory responses and suppress oxidative stress. This review encompasses the most recent evidence in the anti-obesity effect of phenolic compounds from plants to different nutraceuticals and functional foods based on the *in vitro, in vivo* and clinical studies. For that, this review has been focused on popular plant-based products highly consumed today such as cocoa, cinnamon, and olive oil, beverages such as red wine, tea (green, white and black tea) and *Hibiscus sabdariffa* L. tea, among others.

KEYWORDS

Obesity; metabolic syndrome; phenolic compounds; natural products; clinical trials

1. Introduction

The World Health Organization (WHO) has considered obesity as a global epidemic of developed world (World Health Organization. 2000). Varying with ethnicity, overweight and obesity are arbitrarily defined via the body mass index (BMI), a simple weight-for-height relationship (kg/m^2): a BMI $\geq$ 25 being overweight, BMI $\geq$ 30 obesity and morbid obesity (currently type III obesity), when BMI is $\geq$ 40 kg/m^2 (World Health Organization. 2015, Basterra-Gortari et al. 2011). Obesity is a multifactorial disease influenced by behavioral, genetic and environmental factors, the latest being correlated to the economic and social status and lifestyle. Obesity is characterized by an excess of calories consumption together with low energy expenditure, fact that commonly occurs in sedentary lifestyles. Obesity has demonstrated not only increasing adipose burden but also altering adipose biology as pointed out by previous research carried out with human white adipose tissue that reported adipose inflammation (Howe et al. 2013). During the last years, high evidence has emerged associating inflammation and obesity-associated diseases e.g. type 2 diabetes in adults (T2DM), risk of coronary heart disease or dyslipidemia by increasing triglycerides (TG) and decreasing the levels of high density lipoprotein (HDL) cholesterol (Hsu and Yen. 2008, Zeyda and Stulnig. 2009).

Despite the treatment and prevention of obesity need to be multifactorial, among the lifestyle factors, diet is one of the most important one. Dietary habits are continuously changing. In fact, the evolution of food intake since 1964 to nearly present time has evidenced a less intake of vegetables, legumes, cereals, wine and olive oil, whereas there is an increasing intake of meat, fish, beer and, surprisingly, fruits (Contreras Gámez et al. 2014). Globally, these dietary changes can be traduced in lower phenolic compounds intake. In this regard, dietary polyphenols have received tremendous attention among nutritionists, food scientists and consumers due to their roles in human health. Phenolic compounds became a popular research topic since the 1990s due to epidemiological studies indicating an inverse association between the intake of food rich in phenolic compounds and the incidence of some diseases such as cardiovascular disease (CV) or cancer (Visioli et al. 2011). In addition, epidemiological and interventional nutritional studies have shown an inverse association between a polyphenol-rich diet and the prevalence of obesity (Kris-Etherton et al. 2002).

Given the increasing clinical and economic load of obesity, the identification of cost-effective approaches for obesity management becomes crucial (Schwander et al. 2016). Thus, potential strategies include weight reduction, exercise, and suppression of obesity-driven signaling pathways using pharmaceutical or dietary agents (Howe et al. 2013). Traditionally, nutritional therapy has been focused on the saturated fats or carbohydrates reduction. However, new light has been shed on phenolic compounds intake as target anti-obesity compounds.

In this review, we aimed to discuss the *in vitro* and *in vivo* anti-obesity effect of phenolic compounds, studies on humans that reaffirm the latter studies, and the mechanisms underlying their beneficial effect.

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2. Obesity worldwide status: An overview

Non-communicable diseases were responsible for 68% of all deaths globally in 2012, up from 60% in 2000, according to data provided by the WHO (World Health Organization. 2015). Among them, obesity is considered a multifactorial and preventable complex disease that affected more than 600 million people worldwide in 2014. Its prevalence has been increasing for the past 30 years and it is expected to increase 33% over the next two decades, thus, rising up to 51% population and supposing a healthcare cost of $549.5 billion (Finkelstein et al. 2012). Obesity is simply defined as abnormal or excessive fat accumulation in the adipocytes due to adipocyte hypertrophy and hyperplasia (Wang et al. 2014). However, its etymology goes further implying a phenotype primarily associated with excess adiposity, or body fatness, that can manifest metabolically and not just in terms of body size (Hruby and Hu. 2015). Despite it controversy, a strong genetic component to BMI and the risk of obesity has been reported (Guenard et al. 2013, Perusse et al. 2014). However, obesity should not be considered as a single factor due to its prevalence is highly related to diet and lifestyle that promote positive energy balance.

It is noteworthy to highlight that obesity implies an inflammatory response that will alter the immune response (Berg and Scherer. 2005, Blancas-Flores et al. 2010). Adipose tissue is an endocrine and complex organ made up fibroblasts, preadipocytes, adipocytes, vascular constituents and macrophages. Despite the latest has been reported to be closely related to inflammatory process, adipocytes has also recently demonstrated their inflammatory effects through the production of several adipokines which are increased in obesity (Trayhurn and Wood. 2004, Cantley. 2014). The chronic low-grade inflammation derived from obesity has been designed as *metabolic-trigged inflammation* or *metainflammation* (Izaola et al. 2015, Monteiro and Azevedo. 2010) and it has demonstrated to generate associated metabolic syndrome (MS) disorders. MS is referred to the clustering of insulin resistance, hypertension, dyslipidemia, and obesity, and this condition has been associated with increased risk of CV and type 2 diabetes (T2DM) in adults (Mirza and Yanovski. 2014). Overweight and obesity are responsible for about 80% of cases of T2DM, 35% of ischemic heart disease and 55% of hypertensive disease among adults in Europe (Tsigos et al. 2008). This status is in many cases reversible and can be prevented mainly through diet and in lesser extent by physical activity (Heilbronn et al. 2001, Nicklas et al. 2004, Bruun et al. 2006). For that reason, many efforts have been implemented by the Institutions in order to prevent obesity through many strategies that are mainly focused on supporting healthy eating and active living. In this way, new functional formulations (nutraceuticals and functional foods/beverages) based on natural products and containing anti-obese compounds may be acceptable products to face overweight.

3. Nutraceuticals and functional foods: Phenolic compounds as bioactive molecules. The foods for the future world?

The concept of a healthy diet has been changing over recent years. In the industrialized world, due to new challenges from increased costs of health care, longer life expectancy, new scientific knowledge, and the development of new technologies, consumers' interest in healthy eating is moving food, nutrition and biochemical sciences to design products that promote optimal health and reduce the risk of disease, allowing a higher quality of life (Roberfroid. 2000). In this context, the development of nutraceuticals and functional foods has emerged as a promising tool for preventing nutrition-related diseases and improve physical and mental well-being of consumers. Currently, the interest in nature as a source of potential therapeutic agents is increasing. In fact, some authors have reported that natural products and their derivatives represent more than 50% of all the drugs in clinical use in the world. Higher plants contribute over 25% of the total (Gurib-Fakim. 2006) mainly due to its content in phenolic compounds.

Phenolic compounds constitute one of the major groups of nonessential dietary components produced by plants as secondary metabolites under normal and stress conditions. Their structure is characterized by possessing one or more aromatic rings with one or more hydroxyl groups. So far, more than 8000 phenolics with very diverse chemical structures have been identified (Velderrain-Rodríguez et al. 2014). Phenolic compounds have been traditionally employed as food colorants; however, they become a popular research topic since the 1990s due to epidemiological studies indicating an inverse association between the intake of food rich in phenolic compounds and the incidence of some diseases such as cardiovascular diseases or cancer, as commented before (Visioli et al. 2011). Among the main families of phenolic compounds, we can distinguish between flavonoids, which are polyphenolic compounds made up fifteen carbons with two aromatic rings connected by a three-carbon bridge, and non-flavonoids, being phenolic acids the most representative of the diet. Among phenolic compounds, epigallocatechin gallate, resveratrol, catechin, quercetin, procyanidins and anthocyanins are those that are generating more interest for their anti-obesity properties. Fig. 1 depicts their structures.

Several attempts have been carried out to estimate the quantity of dietary phenolic compounds consumed by using i.e. 24-hour dietary recall, individual food consumption records, food-frequency questionnaires (Witkowska et al. 2015, Grosso et al. 2014, Hakim et al. 2001), and extrapolating the data with several databases such as United States Department of Agriculture (USDA) database combined of flavonoid and isoflavone databases, and the Phenol-Explorer database (Rothwell et al. 2013, Perez-Jimenez et al. 2011, Halvorsen et al. 2006). In addition, recently, the possibility of providing dietary intake recommendations such as an adequate intake (AI) for some bioactive food components (e.g. flavonoids) has been discussed (Nielsen. 2014). Ríos-Hoyo et al. (2015) included in their review estimated flavonol consumption of ~25 mg/day in the US, ~20 mg/day in Spain and ~35 mg/day in Asia (Ríos-Hoyo et al. 2015). However, entering polyphenol values into the food composition database and several factors i.e. part of the food consumed, cultivar, processing, storage or cooking methods, among others, interfere in the phenolic composition of foods (Williams et al. 2013). Normally, these studies have been performed in general population. Focus on obese people, this type of studies could be of help in understanding the potential of

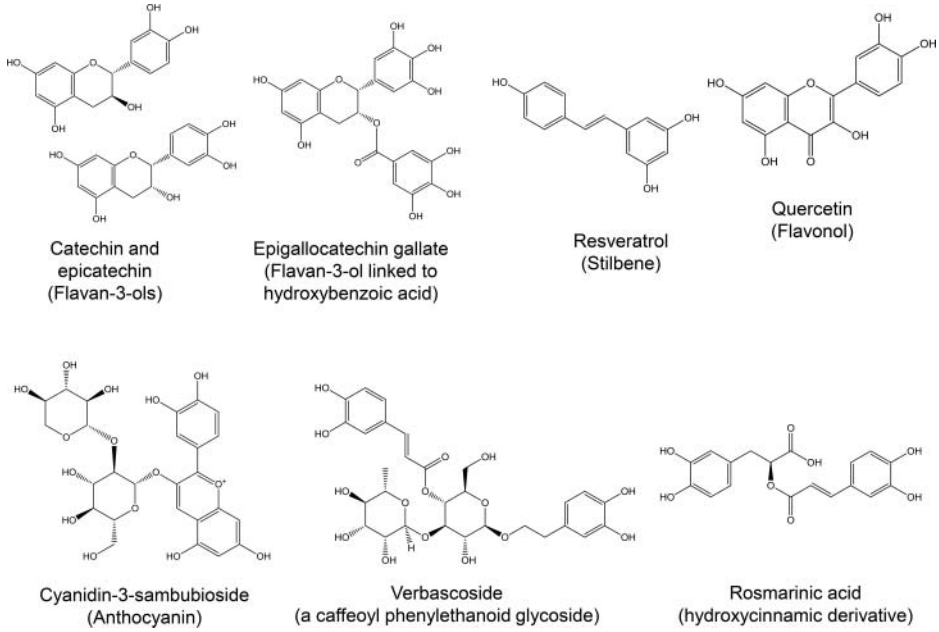

Figure 1. Structure of the most studied phenolic compounds with anti-obesity properties.

some foods to manage overweight as well as to formulate future functional foods/beverages. Nevertheless, this requires a big effort for scientists and administrations. For that reason, in this review we have focused on the existing scientific knowledge about the anti-obese effect of plant-products and beverages consumed today, among others plants matrices, and their derived extracts.

4. Phenolic compounds in non-communicable diseases: Obesity as a target disease

Due to diet and exercise alone are often unsuccessful, many efforts are carrying out for preventing obesity and related-diseases from childhood (Larson et al. 2011) and numerous trials have been conducted in order to develop new anti-obesity drugs (Vasudeva et al. 2012). On this subject, sufficient evidence on phenolic compounds for the management of non-communicable diseases such as cancer, obesity and obesity-related complications has been well documented over the last decade (Park et al. 2015, Hsu et al. 2008, Valls et al. 2016, Lin et al. 2007, Fresco et al. 2006). Wang et al. (2014) encompassed some of the most studied mechanisms for preventing obesity through polyphenols intake i.e. lowering food intake, decreasing lipogenesis, increasing lipolysis, stimulating fatty acids (FA) β-oxidation, inhibiting adipocyte differentiation and growth, and attenuating inflammatory responses and suppress oxidative stress (Wang et al. 2014).

4.1. *In vitro and in vivo studies of phenolic compounds with anti-obesity properties*

4.1.1. *Studies on plant extracts performed in vitro*

Not far from the past, recent investigations in plant and food sciences have been directed towards the identification of natural alternatives to synthetic drugs for a wide range of health conditions and diseases. Preventing overweight and obesity is a priority, for which changes in dietary and physical activity patterns could be combined with the consumption of nutraceuticals and functional foods/beverages containing plant bioactives. Their natural character is probably an extra for consumers, but since these products are not a medicine prescribed by a doctor, a concern about their efficacy may exit. In this way, *in vitro* screening methods could be helpful, facilitating a first answer as well as the searching of anti-obesity phytochemicals in a preliminary, faster and cheaper way than using studies with animal models. Therefore, in this subsection *in vitro* assays to identify plants with anti-obesity properties are reviewed, as well as their potential active phenolic compounds (Table 1).

Inhibition of enzymes: Pancreatic lipase, fatty acid synthase, and others. The regulation of FA and triglycerides (TG) metabolism depends on the activity of lipolytic enzymes, such as pancreatic lipase (EC 3.1.1.3, triacylglycerol lipase). This enzyme contributes to lipid digestion by removing FA from the α and α' positions of dietary TG and releasing the products β-monoglyceride and long chain saturated and polyunsaturated fatty acids (Roh and Jung. 2012). The inactivated lipase is unable to hydrolyze fats, which lead to their passage with feces (Sudeep and Prasad. 2014). Thus, the inhibition of the activity of this enzyme is a potential target for the discovery of anti-obesity phytochemicals. These assays commonly use porcine pancreatic lipase (Roh and Jung. 2012, Gondoin et al. 2010, Sergent et al. 2012), and 2,4-dinitrophenyl butyrate (Roh and Jung. 2012), 4-methylumbelliferyl oleate (Sergent et al. 2012) or *p*-nitro-phenyl laurate (Gondoin et al. 2010) as substrates, measuring the resulting hydrolytic products. Using this test, Roh and Jung (2012) have evaluated 400 plants that growth in Korea or Asia (Roh and Jung. 2012). Among them, four extracts showed the highest anti-lipase activity (at 100 μg/mL): *Salicis radicis* cortex bark (38%), *Corni fructus* fruit (34.8%), *Rubi fructus* fruit (32.5%), and *Geranium nepalense* whole grass (31.4%). In a more comparative way, other studies have

Table 1. Bioactivity of plants extracts evaluated *in vitro* with potential anti-obesity effect.

Plant part	Extract type	Bioactive compounds	Bioactivity	Ref.
Green tea and grape seeds	Commercial extracts dissolved in water	Epigallocatechin-3-gallate, kaempferol and quercetin	Inhibition of lipase activity (IC_{50}, 2.8 and 3.8 μg/mL of gallic acid equivalents)	Sergent et al. (2012)
White and green tea	Infusions	Flavan-3-ols, strictinin and digalloyl glucose derivatives	Inhibition of pancreatic lipase (IC_{50}, 22 and 35 μg/mL, respectively)	Gondoin et al.(2010)
Black tea	Black tea extract and a polymerized polyphenol fraction	Thearubigin-rich fraction	Inhibition of pancreatic lipase (IC_{50}, 15.5 and 36.4 μg/mL, respectively)	Uchiyama et al. (2011)
Pomegranate leaves	Ethanol extract/extract containing 10.6% of ellagic acid	Flavonoids, tannins, quinones, and steroid/ triterpenoids and saponins/ellagic acid	Inhibition of pancreatic lipase (IC_{50}, 20.6 μg/mL/not defined)	Adnyana et al. (2014) Lei et al. (2007)
Garcinia mangostana	Ethanol extract of the hulls and isolates	Xanthones and benzophenones	Inhibition of fatty acid synthase (IC50 of isolates, 1.2 to 91.1 μM)	Jiang et al. (2010)
Extra virgin olive oil	Methanol/water (80:20, v/v)	Hydroxytyrosol, dihydroxytyrosol, together other secoiridoids, including 3,4-DHPEA-EDA and *p*-HPEA-EDA, were the main constituents	Inhibitory activity against α-amylase (IC_{50} 258->2000 μg/mL), α-glucosidase (IC_{50} 189–766 μg/mL) and angiotensin-converting enzyme (98.6–164 μg/mL)	Loizzo et al. (2011)
Hibiscus sabdariffa calyces	Aqueous extracts and fractions	Delphinidin- 3-sambubioside, cyanidin-3-sambubioside, chlorogenic acid and tetra-*O*-methyljeediflavanone, glycosylated flavonols, such as quercetin-3-sambubioside and myricetin-3- glucoside, among others.	3T3-L1 cells and in hypertrophic and insulin resistant adipocyte. The extract nhibited adipogenic differentiation of 3T3-L1 cells: fibre and/or polysaccharides were either inactive or interfered in the model. The extract was more efficient at reducing TG accumulation in insulin-resistant adipocytes than in mature adipocytes. The generation of endogenous ROS was also reduced in this cell model, as well as adipokines levels in insulin-resistant adipocytes	Herranz-Lopez et al. (2012)
Lemon verbena leaves	Aqueous extract and isolated verbascoside	Verbascoside and other phenolic compounds	3T3-L1-adipocyte model: decreased lipogenesis, enhanced FA oxidation and the activation of the energy sensor AMPK	Herranz-Lopez et al. (2015)
Cocoa	Aqueous ethanol (50:50, v/v) and extracted with styrene-based adsorption resin	Not defined	Reduction of adipogenesis and lipid accumulation in 3T3-L1 adypocites without diminishing cell viability. Reduction of protein expression levels of PPARg and C/EBPα, and blocking MCE of preadipocytes by reducing proliferating signaling pathways. Suppression induced phosphorylation of ERK and Akt, and their downstream signals	Min et al. (2013)
Ilex paraguariensis (mate) *leaves*	Aqueous ethanolic (30:70, v/v) extracts and isolated fracgtions using molecular permeation (Sephadex LH-20®)	Rutin, among other phenolic compounds.	Anti-adipogenic activity: 373-L1 adipocytes. Inhibition of TG and modulatory effect on the expression of genes related to the adipogenesis as PPARγ2, leptin, TNF-α and C/EBPα. Also, maté extracts did not display citotoxicity	Gosmann et al. (2012)
Vaccinium floribundum and Aristotelia chilensis	Phenolic extracts from the berrys of both plants, and the commercial powder of *V. floribundum*	Proanthocyanidin-enriched fraction from *V. floribundum*	Reduction of adipogenesis and lipid accumulation in 3T3-L1 adypocites at maturity and when treated throughout differentiation. *V. floribundum* increased Pref-1 expression in preadipocytes. Anti-inflammatory properties on RAW 264.7 macrophages: inhibition of the expression of LPS-induced iNOS/NO and COX-2/PGE2 pathways.	Schrekinger et al. (2010)

Akt, protein kinase B; AMPK, 5′-AMP-activated pro- tein kinase; C/EBPα, CCAAT/enhancer binding protein; COX-2/PGE2, cycloxygenase-2/prostanglandin E2; ERK, extracellular signal-regulated kinase; FA, fatty acids; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MCE, blocking mitotic clonal expansion; PPARγ2, peroxisome proliferator activated receptor gamma 2; PPARα, peroxisome proliferator activated receptor-α; ROS, reactive oxygen species; TG, triglycerides; TNF-α, tumor necrosis factor and.; Pref-1, preadipocyte factor.

estimated the IC_{50} value (concentration resulting in 50% inhibition) of extracts and infusions of grape seed (*Vitis vitivinifera*) (Sergent et al. 2012), white (Gondoin et al. 2010), green (Gondoin et al. 2010,Sergent et al. 2012) and black tea (Uchiyama et al. 2011) (*Camellia sinensis*), and pomegranate (*Punica granatum*) leaves (Adnyana et al. 2014, Lei et al. 2007). All of them are potential anti-obesity agents. Sergent et al. (2012) have also employed a more physiologic *in vitro* method by measuring the rate of release of oleic acid from triolein using pancreatin solution from porcine pancreas, which contains lipase and other enzymes such as trypsin, amylase, etc. (Sergent et al. 2012). They found that in such conditions resveratrol, epigallocatechin-3-gallate and quercetin reduced the triolein digestion to ±50% and so could delay FA absorption *in vivo*.

Other potential target to be studied is the fatty acid synthase (EC 2.3.1.85), a multy-enzyme protein that catalyzes the *de novo* synthesis of saturated FA from acetyl-CoA and malonyl-CoA in the presence of the reducing substrate NADPH (Jiang et al. 2010, Wakil. 1989). Jiang et al. (2010) have evaluated the activity of *Garcinia mangostana* hulls, containing xanthones and benzophenones that could be promising inhibitors of this enzyme (Jiang et al. 2010).

In addition, since overweight and obesity increase the risk of cardiovascular disease and type 2 diabetes mellitus, recent studies have also been focused on other potential therapeutic targets. In this regard, retarding the action of gastrointestinal carbohydrate hydrolyzing enzymes may delay carbohydrate digestion, prolong carbohydrate digestion time, as well as decrease the rate of glucose absorption (Olaokun et al. 2013, Oboh et al. 2014). Following this hypothesis, Olaokun et al. (2013) have screened ten *Ficus* species in order to study the inhibition of α-amylase and α-glucosidase (Olaokun et al. 2013). Among them, the IC_{50} against α-amylase for *F. lutea* (9.4 μg/mL) was the highest, but comparable to *F. craterostoma* and *F. natalensis*. In general, the inhibition potency against α-glucosidase was lower for all extracts, showing again *F. lutea* the lower IC_{50} value (290 μg/mL). Another study (Loizzo et al. 2011) has evaluated the inhibitory activity of extra virgin olive oil (EVOO) against the latter enzymes, observing a stronger activity against α-glucosidase with respect to α-amylase. Interestingly, catechins can also interact with enzymes, including α-amylase and lipase, and inhibit their activities in the body, as well as interfere with the emulsification, digestion, and micellar solubilization of lipids (Vuong. 2014), highlighting the interest in plant derived products such as tea, cocoa or cinnamon bark, which contain this type of compounds (Henning et al. 2003, Cádiz-Gurrea et al. 2014, Rao and Gan. 2014). Concerning cardiovascular diseases, finding natural inhibitors of the angiotensin-converting enzyme (ACE, EC 3.4.15.1) is quite interesting. This enzyme is implied in the regulation of blood pressure through its action on the renin–angiotensin system, converting angiotensin I to angiotensin II that is a potent vasoconstrictor. It also takes part in the kinin–kalicrein system by hydrolyzing the vasodilator bradykinin (Hernández-Ledesma et al. 2011). As an example, Loizzo et al. (2011) have evaluated the inhibition of this enzyme by different EVOO extracts, with IC_{50} values ranging from 98.6 to 164 μg/mL (Loizzo et al. 2011). Among their constituents, hydroxytyrosol, and dihydroxytyrosol were the main phenolic constituents, but 3,4-DHPEA-EDA, *p*-HPEA-EDA and luteolin has shown lower IC_{50} values (Gómez-Navarro. 2009).

Alternatively, other way for studying potential anti-obesity phenolic compounds is through *in silico* investigations of the interaction between phenolic compounds and enzymes. For example, Sudeep and Shyam Prasad (2014) has shown through computational studies that pomegranate leaves phenolics such as punicalagin, corilagin, punicalin and apigenin can interact with catalysis-dependent residues of lipase, making them potential inhibitors (Sudeep and Prasad. 2014). Studying different enzymes, these studies could give clues about a multitarget potential of plant derived phenolic compounds.

Cell models. Obesity is strongly associated with changes in the physiological function of adipose tissue, leading to insulin resistance, chronic inflammation, and altered secretion of adipokines (van Kruijsdijk et al. 2009). Reactive oxygen species (ROS) contribute to both the onset and the progression of insulin resistance (Han. 2016). In order to understand biochemical mechanism undergoing obesity, the cell culture model 3T3-L1 is one of the most reliable models for studying the conversion of preadipocytes into adipocytes (Takahashi et al. 2008), adipogenesis and the biochemistry of adipocytes (Zebisch et al. 2012). As prodifferentiative agents, authors have used insulin, dexamethasone, and 3-isobutyl-1-methylxanthine (Roh and Jung. 2012, Zebisch et al. 2012, Min et al. 2013, Herranz-López et al. 2015). After 4 days adding these agents, the cells start accumulating lipids in the form of lipid droplets, which grow in number and size during culture time (Zebisch et al. 2012). Moreover, the expression of adipokines is also observed during the differentiation process (Takahashi et al. 2008), as well as increasing the incubation time hypertrophied, insulin-resistant adipocytes may be obtained (Herranz-López et al. 2012). In this case, this experiment enables to explore the effects of anti-obesity agents in the context of insulin resistance, similar to that observed in the adipose tissue of obese patients (Takahashi et al. 2008, Herranz-López et al. 2012, Yeop Han et al. 2010).

As an example, Herranz-Lopez et al. (2012) have evaluated the effect of *Hibiscus sabdariffa* (roselle, karkade) aqueous extracts and derived fractions in mature adipocytes of the 3T3-L1 cells and hypertrophied, insulin-resistant adipocytes. *H. sabdariffa* aqueous extracts were more efficient at reducing TG in insulin-resistant adipocytes than in mature adipocytes (Herranz-López et al. 2012). Moreover, these extracts produced a significant inhibition of lipid accumulation and adipogenic differentiation of pre-adipocytes and in the number of differentiated cells, as well as the reduction in the accumulation of TG. *H. sabdariffa* extract reduced ROS levels in hypertrophied adipocytes and inhibited the secretion of adipokines, including leptin and MCP-1, which are implied in the regulation of the migration of non-resident macrophages to the adipose tissue. In a similar way, other matrices studies using this model were lemon verbena (*Lippia citriodora*) (Herranz-López et al. 2015), cocoa (*Theobroma cocoa*) (Min et al. 2013), mate (*Ilex paraguariensis*) (Gosmann et al. 2012), *Vaccinium floribundum* and *Aristotelia chilensis* (Schreckinger et al. 2010) (Table 1).

Since obesity is associated adipose tissue inflammation (Yeop Han et al. 2010), studies on lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages are helpful to evaluate the

anti-inflammatory properties of plant extracts. These cells are very sensitive to LPS stimulation, producing the activation of pro-inflammatory transcription factors, nuclear factor-kappaB and activator protein-1, tumor necrosis factor-alpha, interleukin-1beta, nitric oxide (NO) production, etc. (Bognar et al. 2013). Using this cell line, Schrekinger et al. (2010) have shown that *V. floribundum* and *A. chilensis* extracts decreased the production of nitric oxide and prostaglandin E2, as well as the expression of inducible NO synthase and cycloxygenase-2 (Schreckinger et al. 2010).

4.1.2. Studies on plant extracts performed in animal models

Some of the plants described above have shown not only bioactivity *in vitro*, but also their anti-obesity properties have been demonstrated in animal models: grape seeds (Décordé et al. 2009), and also wine (Agouni et al. 2009, Bargalló et al. 2006, Gourineni et al. 2012); tea (Uchiyama et al. 2011); lemon verbena leaves (Herranz-López et al. 2015); pomegranate leaves (Lei et al. 2007), fruits, juice and seed oil (de Nigris et al. 2007); cocoa (Min et al. 2013, Rabadan-Chávez et al. 2016); olive oil (Ebaid et al. 2010) and also leaves (Shen et al. 2014); *H. sabdariffa* (Villalpando-Arteaga et al. 2013). Other potential anti-obesity extracts has been obtained from Cornelian cherry (*Cornus mas*) (Jayaprakasam et al. 2006), cinnamon (*Cinnamomum zeylanicum*) (Sartorius et al. 2014), and fig plant (*Ficus carica)* (Belguith-Hadriche et al. 2016, Belguith-Hadriche et al. 2017). In this regard, Table 2 describes plant extracts tested *in vivo*, their potential bioactive compounds, selected animal model, mechanisms of action and administered dose. The animal models used were C57BL/6 mice, Zucker lean rats (Fa/Fa), Wistar rats, and Syrian Golden hamster fed a high-fat diet, as well as obese Zucker rats. The latter is a spontaneous genetic model of obesity that exhibits hyperphagia, hyperlipidemia, and hyperinsulinemia (Oana et al. 2005). This is also considered a model of metabolic syndrome, and as well some colonies can develop hypertension (Agouni et al. 2009), so it may give clues not only about obesity, but also about other comorbid conditions.

Although the mechanisms of action depend on the studied extract and the animal model, a general event is the reduction of animal body weight, fat tissue and energy intake. Moreover, they may improve glucose metabolism by reducing plasma glucose, and ameliorate hyperlipidaemia, being able to reduce levels of TG, TC and LDL-cholesterol in plasma. Plant extracts can act enhancing NO bioavailability as a result of an increase of NO, eNOS activity, and/or reduction of superoxide anion production (Lin et al. 2007, Uchiyama et al. 2011, Min et al. 2013, Herranz-López et al. 2015, Décordé et al. 2009, Agouni et al. 2009, Bargalló et al. 2006, Gourineni et al. 2012, Villalpando-Arteaga et al. 2013) (Table 2). Another studies also suggests other mechanisms; as an example, an olive leaves extract was able to regulate the expression of genes involved in adipogenesis and thermogenesis in the visceral adipose tissue (Shen et al. 2014), while olive oil could enhance fat oxidation and regulate myocardial metabolic enzymes, that lead to optimize cardiac energy metabolism (Ebaid et al. 2010). In addition, the supplementation with pomegranate fruit extract or juice was able to decrease the expression of vascular inflammation markers, thrombospondin, and cytokine TGFbeta1 (de Nigris et al. 2007), whereas cinnamon extract improved insulin sensitivity in the brain (Sartorius et al. 2014). In another study, the administration of cocoa powder and a cocoa extract was associated with adipogenesis, β-oxidation and energy expenditure linked to upregulating the expression of genes involved in the regulation of lipid metabolism, peroxisome-proliferator-activated receptor γ (PPARγ), PPARα, PPARγ coactivator 1α (PGC1α), sirtuin 1 (SIRT1) and uncoupling protein 1 (UCP1), decreasing TNF-α and increasing anti-inflammatory adipokines (ApN) levels in white adipose tissue (Rabadán-Chávez et al. 2016).

As active constituents, the latter studies have highlighted that phenolic acids, flavonols, flavan-3-ols (Décordé et al. 2009, Rabadan-Chávez et al. 2016), anthocyanins (Gourineni et al. 2012, Villalpando-Arteaga et al. 2013, Jayaprakasam et al. 2006), verbascoside (a caffeoyl phenylethanoid glycoside) (Herranz-López et al. 2015), secoiridoids (Ebaid et al. 2010), as well as furanocoumarins (Belguith-Hadriche et al. 2017) could participate in the beneficial effect of the plant extracts against obesity and its comorbid conditions. Anyway, a synergic effect should not be ruled out since plant extracts are complex.

Just as a note, in order to reduce body fat, changes in lifestyle by means of caloric restriction intake or increased caloric expenditure are sometimes difficult to achieve by people. Plant containing anti-obesity polyphenols may provide a similar effect without restricting caloric intake (Herranz-López et al. 2012). It is worth mentioning that some of the aforementioned studies have been performed in plants use for making beverages and infusion, and thus consumed worldwide as a daily habit, such as tea, wine, and Hibiscus tea. Furthermore, other interesting product is virgin olive oil, the main fat consumed in the popular and healthy Mediterranean Diet (Contreras Gámez et al. 2014). For this reason, finding the active molecules and the required minimum dose to produce the anti-obesity effect in humans is crucial. Nevertheless, we should have in mind that the amount of sugar addition in infusions should be controlled if large volume is consumed daily (Vuong. 2014).

4.2. Clinical studies: Anti-obesity effect of phenolic compounds and vehicle (plant extract/fraction, nutraceutical and food)

Despite the widespread use of putatively antidiabetic, antihypertensive and cholesterol-lowering botanical supplements, few botanicals have been effectively evaluated in controlled clinical trials using well-characterized agents (Graf et al. 2010). The anti-obesity effects, however, are being investigated with promising positive results. In this regard, several phenols-rich plant extracts have been studied by a number of human clinical trials (Table 3).

One of the most studied rich-phenol matrixes involved in anti-obesity effect is green tea and derived extracts. In fact, excellent reviews have focused on the explanation of its possible mechanism of action (Wolfram et al. 2006, Rains et al. 2011, Huang et al. 2014, Suzuki et al. 2016). Despite the appreciable number of trials that apparently support the anti-obesity effects of green tea, it has not been stablished a suitable fixed dosage of green tea catechins (GTC). In fact, the dosage of 150 mg capsule of epigallocatechin gallate (EGCG) in overweight/obese post-menopausal women showed inconsistent results regarding

Table 2. Plants extracts with anti-obesity effect in animal models.

Plant extract	Bioactive compounds	Animal model	Mechanisms of action	Daily dose	Ref.
Red wine	Not defined	Zucker lean rats (Fa/Fa) fed a high-fat diet (HFD)	Prevention of metabolic and cardiovascular alterations associated with obesity: Reduction of BW gain, energy intake, and fat mass at epidymal location respect to the whole body weight	Free access to red table wine for 8 weeks	Vadillo Bargalló et al. (2006)
Commercial red wine extract (Provinols™)	70% phenolic compounds (phenolic acids, anthocyanins, flavan-3-ols, flavonols, tannins and the stilbene resveratrol)	Zucker fatty rats (Fa/Fa)	Reduction of plasma glucose and fructosamine, TG, TC and LDL-cholesterol. Improve cardiac performance, corrected endothelial dysfunction in aortas by improving endothelium-dependent relaxation in response to acetylcholine. Moreover, increase of NO production through enhanced eNOS activity and reduced superoxide anion release via decreased expression of Nox-1.	20 mg/kg for 8 weeks	Agouni et al. (2009)
Muscadine grape (*Vitis rotundifolia*) & wine extracted with Amberlite FPX66	Anthocyanins and ellagic acid could contribute	C57BL/6J mice fed a HFD	Decrease of body weights and plasma content of FA, TG, and cholesterol in obese mice. Inflammation was alleviated, activity of glutathione peroxidase was enhanced, and insulin sensitivity was improved. Glucose control in mice.	Supplementation with 0.4% of each extract for 15 weeks	Gourineni et al. (2012)
Chardony grape seed commercial extract (by Partoeno)	Flavan-3-ols, which represents approximately 69%, and comprised of (+)-catechin and (+)-epicatechin.	Syrian Golden Hamster fed a HFD	Reduction of abdominal fat, insulinemia and leptinemia, whereas adiponectin level was increased. Prevention of cardiac production of superoxide anion and NADPH oxidase expression.	≈0.04 g/kg for 12 weeks	Décordé et al. (2009)
Polymerized polyphenol fraction (BTPE) from Black tea	Not clarified	–Wistar rats –Female C57BL/6N mice fed a HFD	–Reduction of the increased plasma TG levels. –5% BTPE suppressed increases in BW, parametrial adipose tissue mass, and liver lipid content.	−0.5 – 1 g/kg (wistar rats) in a lipid emulsion –Feed supplemented with 1% or 5% (w/w) BTPE for 8 weeks	Uchiyama et al. (2011)
Lemon verbena extract	Verbascoside and other phenolic compounds	LDL receptor-deficient male mice in a C57BL/6J background (LDLr−/−) fed with a high-fat, and HFD	Prevention of the expected gain in BW, decrease in the weight of most organs and tissues and epididymal and inguinal white adipose tissue. Reduction of plasma TG and cholesterol levels, the accumulation of neutral lipids and triglycerides in the liver without altering serum biomarkers of hepatic toxicity	0.75 g/kg for 14 weeks	Herranz-Lopez et al. (2015)
Pomegranate leaves	Ellagic acid	HFD induced obese ICR mice	Decrease in BW, energy intake and several adipose pad weight percents and serum, TC, TG, glucose levels and TC/HDL-cholesterol ratio. Reduction of the appetite.	0.8 g/kg for 5 weeks treatment	Lei et al. (2007)
Pomegranate extracts from fruit (PFE), juice (PJ) and seed (PSO) oil	Not defined	Obese Zucker rats	The supplementation with PFE or PJ significantly decreased the expression of vascular inflammation markers, TSP, and cytokine TGFbeta1, while PSO influenced only TSP-1 expression. Plasma NOx levels and eNOS were increased by PFE and PJ.	Diluted in water for 5 weeks	de Nigris et al. (2007)
Cocoa extract	Not defined	Male C57BL/6N mice receiving HFD	Reduction of BW, epididymal fat and liver masses. At 0.2 g/kg attenuated TG.	0.04–0.2 g/kg for 5 weeks	Min et al. (2013)
Cocoa powder (Co-P), cocoa extract (Co-E)	Epicatechin	Wistar rats receiving high fat diet	Upregulation of the expression of genes involved in FA uptake, β-oxidation and energy expenditure in rat white adipose tissue, suggesting an improvement in adipose tissue function with a better capacity to store nutritional overload and to attenuate the production of inflammatory cytokines.	Co-P, 1 g/kg; Co-E, 100 mg/kg; epicatechin, catechin and procyanidin B2 (10 mg/kg) for 8 weeks	Rabadan-Chávez et al. (2016)

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Table 2. (*Continued*)

Plant extract	Bioactive compounds	Animal model	Mechanisms of action	Daily dose	Ref.
Olive oil	Oleuropein, caffeic acid, amon others	Wistar rats receiving hypercaloric-chow	Increased oxygen consumption, fat-oxidation, myocardial beta-hydroxyacyl coenzyme-A dehydrogenase and lower respiratory-quotient. Citrate-synthase was also highest.	3 g/kg for 42 days	Ebaid et al. (2010)
Hibbiscus subdarifa aqueous extract	Delphinidin-3-sambubioside and cyanidin-3-sambubioside	High fat diet-induced obese C57BL/6NHsd mice	Reduction of fat tissue accumulation, BW gain and dyslipidemia, liver steatosis and normalization of the glycemic index. Down-regulation of SREBP-1c and PPAR-γ, avoiding the increase of IL-1, TNF-α mRNA and lipoperoxidation, while catalase mRNA was increased	33 mg of anthocyanins/kg three times a week for 8 weeks	Villalpando-Arteaga et al. (2013)
Cinnamon (*Cinnamomum zeylanicum*) extract	Not defined	C57BL/6J fed with a HFD	No significant effect in BW or fat accumulation, but the brain response to insulin was ameliorated. Tyrosine phosphorylation of insulin receptor and AKT was improved and insulin-stimulated PTP-1B expression was diminished. In addition, cinnamon did not affect fasted plasma blood glucose levels.	Drinking water supplemented with the extract (0.8 g/kg)	Sartorius et al. (2014)

AKT, protein kinase B; BW, body weight; HFD, high-fat diet; eNOS, endothelial NO-synthase; IL-1, interleukin-1; LDL-cholesterol, low density lipoprotein-cholesterol; Nox-1, NADPH oxidase membrane sub-unit 1; SREBP-1c, sterol regulatory element-binding protein-1c; TC, total cholesterol; TG, triglycerides; TSP, thrombospondin; PPAR-γ, peroxisome proliferator-activated receptor gamma.

Table 3. Clinical studies based on the phenolic compounds rich extract consumption.

.Matrix	Bioactive compound	Study design	n	Mechanisms of action	Ref.
Chocolate	Not defined	Each subject was asked to complete a visual analogue scale (VAS) designed to assess appetite (t = 0). After that, they were requested to eat a standard 30 g portion of dark chocolate (85% cocoa) and to complete a VAS at 5, 10, 20, 30, 40, 50 and 60 min, each time swiftly followed by blood sampling and measurement of gallbladder volume.	12	More satiation and fullness and less appetite and hunger after chocolate eating compared to control ($p<0.01$). No significant changes in glucose, insulin, GLP-1, ghrelin, CCK and gallbladder	Massolt et al. (2010)
	Not defined	Cross-sectional study in which subjects responded to the question "How many times a week do you consume chocolate? Amount of chocolate consumed (vs frequency with which it was consumed) was also examined.	1017	>Chocolate consumption frequency, <BMI ($p = 0.01$). No statistical correlation were found between chocolate consumption frequency and BMI ($p = 0.97$)	Golomb et al. (2012)
	Catechin and epicatechin	Stage 1 hypertensives and overweight volunteers consumed 50 g of chocolate 70% cocoa/day (2135 mg polyphenols) for 4 weeks	22	No significant changes in anthropometric parameters, percentage body fat, glucose metabolism, lipid profile, biomarkers of inflammation, adhesion molecules, oxidized LDL, and blood pressure in pre and post-intervention. ↑in reactive hyperemia index ($p = 0.01$).	Nogueira et al. (2012)
	Not defined	Randomized crossover study. 100 g of dark chocolate or milk chocolate consumed by healthy and normal weigh men. Visual-analogue scales were used to record appetite sensations before and after the test meal was consumed and subsequently every 30 min for 5 h. An *ad libitum* meal was served 2 h after the test meal was consumed.	16	↓ 17% energy intake at the ad libitum meal after consumption of the dark chocolate than after the milk chocolate ($p = 0.002$).	Sorensen et al. (2011)
Grape extract	Resveratrol	Triple-blind, randomized, placebo-controlled trial consisted on group 1: 1 capsule/day (350 mg) for 6 months of GE enriched in reverastrol (GE-RES, Stilvid®); group 2: 1 capsule/day (350 mg) for 6 months of GE NO enriched in reverastrol or group 3:placebo.	75	↓LDLc (4.5%, p = 0.04), ↓ApoB (9.8%, $p = 0.014$), ↓LDLox (20%, $p = 0.001$), and ↓LDLox/ApoB (12.5%, $p = 0.000$) decreased in the Stilvid® group, ↑the ratio non-HDLc/ApoB (8.5%, $p = 0.046$). ↓LDLc by 2.9% ($p = 0.013$) in the GE group	Tome-Carneiro et al. (2012)
Grape pomace and omija fruit ethanol extracts (GO)	Not defined	Randomized, placebo-controlled trial consisted on the intake of group1: low-GO (low dose GO, grape pomace extract [342.5 mg/day] + omija fruit extract [57.5 mg/day]), Group 2: high-GO (high dose GO, grape pomace extract [685 mg/day] + omija fruit extract [115 mg/day]) and group 3: placebo for 10 weeks	76	No significant changes in the body weight and body fat of overweight or obese subjects was not significantly altered in the low-GO and high-GO groups.Significant ↓ in TC, LDLc, HDLc, apo B, apoB/apoA-1, Lp(a) plasma levels, ↑ apo-A 1 and ↓ atherogenic index, IL-1β, tumor necrosis factor-α, and elevated erythrocyte antioxidant capacity in high-GO compared to control group.	Han et al. (2016)
Green tea extract	EGCG	Randomized, double-blind, placebo-controlled clinical trial in obese women with BMI > 27 kg/m2 One capsule (400 mg) green tea extract (491 mg catechins containing 302 mg EGCG). 3 times/day 12 weeks.	78	Not significant reduction of BW, WC or BMI between control and interventional groups. ↓ LDLc ($p = 0.1$) and TH ($p = 0.06$), and marked but not significant increase in the level of HDLc, adiponectin and ghrelin.	Hsu et al. (2008)
	EGCG	Randomized controlled trial in healthy volunteers with BMI between 25 and 32 kg/m2. Each subject received 2 times/d (i.e. 2 capsules morning, 2 capsules midday) a green tea extract AR25®; ingestion of 4 capsules containing AR25 provided a daily total of 375 mg catechins, of which 270 mg was epigallocatechin gallate for 3 months	70	↓ BW 4.6% and WC by 4.48% in AR25 group.	Chantre and Lairon (2002)
	EGCG	Randomized, double-blind trial in women with central obesity who received high-dose green tea extract at a daily dosage of 856.8 mg for 12 weeks.	115	↓ Weight loss ($p = 0–025$), BMI ($p = 0.018$), WC ($p = 0.023$), TC r($p = 0,005$), and LDLc ($p = 0.006$) plasma levels	Chen et al. (2016)

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Table 3. (*Continued*)

.Matrix	Bioactive compound	Study design	n	Mechanisms of action	Ref.
	Catechins	In a double-blind, placebo-controlled trial, obese, hypertensive subjects were randomized to receive a daily supplement of 1 capsule that contained either 379 mg of GT extract (GTE) or a matching placebo, for 3 months.	56	↓ in fasting serum glucose and insulin levels and insulin resistance ($p<0.01$), ↓ TG, TNF-α, CRP, TAS, HOMA-IR ($p<0.001$); ↓ LDLc ($p = 0.022$), ↑ HDLc ($p = 0.023$) plasma levels.	Bogdanski et al. (2012)
Hibiscus sabdariffa extract	Anthocyanins	Randomized, double-blind trial in adults with BMI ≧ 27 kg/m2 who consumed 2 HSE capsule-dose after meals, 3 times a day (one dose of a HSE treatment capsule contains 450 mg HSE extract and 50 mg starch) for 12 weeks	44	↓ body weight ($p = 0.008$), BMI ($p = 0.009$), body fat ($p = 0.16$) and the waist-to-hip ratio ($p = 0.010$)	Chang et al. (2014)
	Not defined	*H. sabdarifa* calices 125 mg/kg/day for 4 weeks in patients with metabolic syndrome	31	Improved antioxidant status (↓levels of circulating 8-isoprostane-F2α ($p = 0.019$) and ↑ serum paraoxonase activity ($p = 0.049$)), ↓ TC ($p = 0.020$), ↑HDLc ($p = 0.040$) and ↓ inflammatory markers TNF-α ($p = 0.049$), IL-6 ($p = 0.043$), IL-1ß ($p = 0.031$), IL-8 ($p<0.05$), CCL2 ($p = 0.042$)	Joven et al. (2014)
	Not defined	A factorial, randomized, follow-up study in volunteers with MS. Daily oral ingestion of a capsule containing 100 mg HSE before breakfast for a month	222	↓ Glucose ($p<0.05$), TC ($p<0.05$), and LDLc ($p<0.05$) levels, ↑ HDLc ($p<0.001$) levels in ME patients	Gurrola-Díaz et al. (2010)
	Not defined	Double blind, placebo controlled, randomized trial subjects with serum LDL values in the range of 130–190 mg/dl and with no history of coronary heart disease. Two 500 mg capsules daily (1 g/day) for 90 days	60	No significant changes in body weight ($p = 0.84$); BMI ($p = 0.73$); WC ($p = 0.21$) or percent fat ($p = 0.07$)	Kuriyan et al. (2010)
Berries	Anthocyanins	8 weeks randomized controlled trial in obese men and women with ME who consumed 50 g freeze-dried blueberries, ~350 g fresh blueberries daily	48	↓ in systolic and diastolic blood pressures (p = 0.05), plasma oxidized LDL and serum malondialdehyde and hydroxynonenal in the blueberry-supplemented group compared to controls ($p = 0.01$). No significant changes anthropometrics, serum glucose concentration and lipid profiles.	Basu et al. (2010)
	Not defined	Randomized cross-over study design in female volunteers with BMI ranged into 26–34 kg/m2. 4 different berry diets. The amount of berries/berry fractions in the berry diets was equivalent to an average daily dose of 100 g fresh berries.	110	↓ after BB ($p = 0.041$) and SB ($p = 0.008$) periods and also a small decrease in weight after BB diet ($p = 0.028$)	Lehtonen et al. (2011)
Rosemary (*Rosmarinus officinalis*) extract	Not defined	Healthy adults were randomly selected and given 2, 5 or 10 g/day of rosemary leaves powder for a period of 8 weeks	48	↓ TC and TG in the three treated groups ($p<0.01$). ↓ LDLc ($p<0.01$) and ↑ HDLc ($p = 0.023$) in the group given 10 g of the herb powder, ↓ fasting serum glucose the group given 5 and 10 g ($p<0.01$).	Labban et al. (2014)
Licorice flavonoid oil *(Glycyrrhiza)*	Glabridin	Ramdomized, double-blind, placebo-controlled study in moderately overweight participants who were asigned in groups for intaking 0 (placebo), 300, 600, or 900 mg of LFO for 8 weeks	84	Total body fat mass decreased significantly ($p<0.05$) in the three LFO groups after 8 weeks of ingestion. LFO (900 mg/day) ↓ visceral fat area, body weight, BMI, and LDLc ($p<0.05$).	Tominaga et al. (2009)
Cinnamon extract	polyphenol type-A polymers	Randomized, placebo-controlled, double-blind clinical trial with two parallel groups with prediabetes and the metabolic syndrome. Each subject was instructed to take two capsules (250 mg) of their respective supplement twice per day (with breakfast and dinner) for 12 weeks (500 mg of Cinnulin PF® is equivalent to ~10 g of whole cinnamon powder).	22	↓in fasting blood glucose ($p<0.01$), sistolic blood pressure ($p<0.001$), and ↑ lean mass ($p<0.002$) pre and post treatment compared with the placebo group. Additionally, within-group analyses uncovered small, but statistically significant ↓ body fat ($p<0.02$) in the Cinnulin PF® group.	Ziegenfuss et al. (2006)

	Not defined	Randomized, placebo-controlled, double-blind clinical trial with patients with diagnosed T2DM not on insulin therapy but treated with oral antidiabetics or diet. 3 g of cinnamon powder per day/3 times/day for 4 months	79	↓fasting plasma glucose level in the cinnamon group (10.3%) than in the placebo group (3.4%) post-intervention. No significant intragroup or intergroup differences were observed regarding HbA1c, lipid profiles or differences between the pre- and post-intervention levels of these variables.	Mang et al. (2006)
	Not defined	Participants with T2DM randomized in groups 1, 2, and 3 consumed 1, 3, or 6 g of cinnamon daily, respectively, and groups 4, 5, and 6 were given placebo capsules corresponding to the number of capsules consumed for the three levels of cinnamon. The cinnamon was consumed for 40 days followed by a 20-day washout period.	60	↓the mean fasting serum glucose (18–29%), TG (23–30%), LDLc (7–27%), and TC (12–26%) levels in 3 cinnamon groups ($p<0.05$). No significant changes were noted in the placebo groups. Changes in HDLc were not significant.	Khan et al. (2003)
	Not defined	A double blind, randomized, placebo controlled clinical trial was conducted on patients with T2DM. Participants were randomly assigned to take either a three g/day cinnamon supplement ($n = 22$) or a placebo ($n = 22$) for eight weeks.	44	↓fasting blood glucose, HbA1c, TG, body weight, BMI, fat body mass ($p<0.05$) after intervention in cinnamon group.	Vafa et al. (2012)
Fraxinus excelsior L. seeds	Not defined	Longitudinal, randomized, crossover, double-blind, placebo-controlled 7-week nutritional intervention. The participants received daily 3 capsules each containing either 333 mg of an extract from *Fraxinus excelsior* L. seeds (Glucevia®) or placebo capsules (control) in a random order for 3 weeks with 1 week of washout between treatments.	22	↓ Incremental glucose area under the curve ($p<0.01$) and 2 h blood glucose values ($p<0.01$) following an oral glucose tolerance test. ↑ adiponectin:leptin ratio ($p<0.05$) and ↓fat mass ($p<0.01$) in Glucevia® group compared to control ($p<0.05$).	Zulet et al. (2014)
Sinetrol-XPur (polyphenolic citrus dry extract)	Not defined	In a 12-week, randomized, double-blind, placebo-controlled trial, Sinetrol-XPur (polyphenolic citrus dry extract) was given to overweight subjects twice daily with meals.	47	↓ WC, hip circumference and abdominal fat in the Sinetrol-XPur group as compared with the placebo group ($p<0.0001$), ↓ Inflammatory markers (C-reactive protein and fibrinogen) ($p<0.01$), ↓ oxidative stress by the reduction of malondialdehyde and ↑ in superoxide dismutase and glutathione ($p<0.01$).	Dallas et al. (2014)

Apo A-1, apolipoprotein A-1; Apo B, Apolipoprotein B; BB, Bilberry; BMI, Body mass index; BW, Body weight; CCK, Cholecystokinin; CCL2, C-C-chemokine ligand 2; CRP, C-reactive protein; EGCG, Epigallocatechin gallate; GE, Grape extract; GLP-1, Glucagon-like-peptide 1; HBA1c, Glycated hemoglobin A1c; HDL-C, High-density lipoprotein; HOMA-IR, homeostasis model assessment–insulin resistance; HSE, *Hibiscus sabdariffa* extract; IL, interleukin; LDL-C, Low-density lipoprotein; LFO, licorice flavonoid oil; Lp(a), lipoprotein A, RES, Resveratrol; SB, sea buckthorn; T2DM, 2 type-Diabetes Mellitus; TAS, Total antioxidant status; TC, Total cholesterol; TG, triglyceride; TNF, tumor necrosis factor α; WC, waist circumference.

the loss of body fat (Hill et al. 2007). More reliable results have been found with higher dosages ranged from 270 to 1200 mg/day (Rains et al. 2011). In this regard, the intake of a total of 375 mg GTC, of which 270 mg was EGCG from a green tea commercial extract reduced body weight by 4.6% and waist circumference by 4.48% in 70 moderately obese patients without changing the lipidic profile (Chantre and Lairon. 2002). However, higher daily doses of EGCG (856.8 mg) significantly reduced weight, body mass index (BMI) and waist circumference in 115 women with central obesity accompanied by a reduction of total cholesterol and low-density lipoprotein plasma levels without compromising the safety (Chen et al. 2016). Bogdanski et al. (2012) also reported significant improvement on the lipidic profile but not significant changes in BMI in a double-blind, placebo-controlled trial in 56 obese hypertensive patients who took 379 mg/ day of GCT (Bogdanski et al. 2012). In the same line were the results published by Hsu et al. (2008) (Hsu et al. 2008). They found only a 0.3% non-significant difference in the body weight between the intervention group (78 obese women), who took 1200 mg/day of green tea extract (302 mg EGCG) during 12 weeks, and the control group. However, the lipidic profile was enhanced via the significant reduction of LDL and triglycerides and the increase of high-density lipoprotein. Although inconsistent, the proposed *in vivo* mechanisms of action of green tea are related to the stimulation of thermogenesis that promotes fat oxidation or inhibition of appetite (Dulloo et al. 1999, Belza et al. 2007). Contrarily, in a randomized, double-blind controlled trial carried out in 83 obese woman who were supplemented with 300 mg/d of EGCG for 12 weeks, no changes in weight lost or body fat composition were found (Mielgo-Ayuso et al. 2014), probably due to the intervention was carried out in Caucasian participants as previously reported by Hursel et al. (2009) (Hursel et al. 2009). Despite the thermogenic effect of green tea was primarily associated with its content in caffeine, several studies have recently demonstrated a combined effect between caffeine and catechin-polyphenols in stimulating brown adipose tissue thermogenesis through the increase of noradrenaline release (Dulloo et al. 2000, Westerterp–Plantenga et al. 2005).

H. sabdariffa extract is being increasingly employed in different beverages and tea forms as anti-obesity agent. Despite most of studies have been carried out *in vitro* and *in vivo*, several clinical trials have reported its anti-obesity effects. Chang et al. (2014) reported a significant decrease in BMI, body weight and waist-to-hip ratio in 19 obese participants who took two capsule-dose of *H. sabdariffa* extract three times a day for 12 weeks compared to control. However, they did not find any significant change in lipid profile (Chang et al. 2014). Contrarily, Joven et al. (2014) showed a significant improvement of HDL and total cholesterol plasma concentrations in 31 patients with metabolic syndrome when administering 125 mg/kg/day of polyphenols from *H. sabdariffa* calices for 6 weeks (Joven et al. 2014). In agreement with the latest study, a randomized controlled trial performed with apparently healthy volunteers who consumed 100 mg of *H. sabdariffa* extract for 4 weeks, showed a significant decrease of total cholesterol, glucose, LDL-c and a significant increase of 37.5% of HDL (Gurrola-Díaz et al. 2010). Contrarily, the consumption of 1 g/day of *H. sabdariffa* leaf extract for 12 weeks did not show any significant change in anthropometric parameters or in lipidic profile of 60 participants (Kuriyan et al. 2010). The anti-obesity effect of *H. sabdariffa* has been attributed mainly to its composition in anthocyanins (Prior et al. 2009), one of its higher components. Concretely, delphinidin-sambubioside and cyanidin-sambubioside are the major anthocyanins characterized in *H. sabdariffa* (Gurrola-Díaz et al. 2010, Ojeda et al. 2010, Alarcon-Aguilar et al. 2007). Nevertheless, despite the promising results showed by this plant, the lack of standardized analytical method for analyzing *H. sabdariffa* phenolic composition and the differences trials designs, make difficult establishing the target phenolic compound and the dosage for achieving optimum results.

Despite the limitation of investigation of the efficacy of berries in improving features of obesity, nutritional epidemiology studies suggest that berries could have a slight effect in obesity and obesity-related pathologies management. In this regard, a berry extract equivalent to a dosage of 100 g of fresh berries during 33–35 days allowed a significant decrease in waist circumference and a small decrease of body weight in 110 overweight women when replacing part of their normal diet with this bilberries extract (Lehtonen et al. 2011). On its behalf, the intake of 50 g freeze-dried blueberries, equivalent to 350 g of fresh blueberries, for 8 weeks, decreased significantly the plasma oxidized LDL concentration without altering the body weight, waist circumference and lipid profile in 48 volunteers with metabolic syndrome (Basu et al. 2010). Several clinical trials carried out using grape extracts have suggested their cardioprotective effect reducing the atherogenic markers or improving the lipidic profile (Kar et al. 2009, Tomé-Carneiro et al. 2012). However, despite, *in vitro* and *in vivo* studies have shown the potential of grape and grape-seed extracts on obesity management (Décordé et al. 2009, Zhang et al. 2012), little is known about its effect in clinical practices. Han et al. (2016) examined the efficacy of grape pomace and omija fruit ethanol extract on metabolic disorders in 76 in overweight or obese subjects with promising results lowering TC, LDL-C and improving HDL-C plasma concentrations. Contrarily, no significant differences in body weight and body fat were found between intervention and control group (Han et al. 2016).

Other rich-phenols medicinal plants such as rosemary (*Rosmarinus officinalis* L) extract (Labban et al. 2014), licorice flavonoid oil (Tominaga et al. 2009), *Fraxinus excelsior* L. (Zulet et al. 2014) and cinnamon extract (Sartorius et al. 2014) showed positive effect in lipid and body fat profile. Concretely, a diet supplementation with 10 g of rosemary leaf extract reduced LDL-C and increased HDL-C in 48 participants and after 8 weeks of intervention (Labban et al. 2014). Among phenolic compounds from rosemary leaves, rosmarinic acid is the predominant one and the bioactivity of this plant has been mainly attributed to its presence (Borrás-Linares et al. 2014). It has been suggested that this compound could be the responsible of the inhibition of pancreatic lipase and hormone sensitive lipase, thus, allowing total cholesterol and LDL-C reduction (Bustanji et al. 2010). Concerning licorice, a randomized, double-blind, placebo-controlled study carried out in 84 moderately overweight participants showed a significant decrease in visceral fat, BMI, body weight and LDL-C when volunteers consumed 900 mg of licorice flavonoids oil (Tominaga et al. 2009). In this

case, hydrophobic flavonoids from *Glycyrrhiza glabra* could increase energy expenditure by enhancing beta-oxidation and inhibits lipogenesis resulting in reduction in body fat and body weight (Tominaga et al. 2009). The intake of 1000 mg of a commercial extract of *F. excelsior* L. (Glucevia®) which provided 4 mg/day of coumarins, allowed a significant reduction of the body fat mass and the and the waist:hip ratio in 22 non-diabetic overweight/obese healthy subjects (50–80 years) (Zulet et al. 2014). Despite several phenolic compounds families have been described in this matrix i.e. secoiridoid glucosides, coumarins, flavonoids, phenylethanoids, benzoquinones, indole derivatives, and simple phenolic compounds (Sanz et al. 2012), the lack of enough clinical trials, make difficult attributing it bioactivity to phenolic compounds. On its behalf, cinnamon is one of the most important spices used daily over the world and it contains high levels of phenolic compounds such as phenolic acids, coumarins, and proanthocyanidins (Wang et al. 2013). Although antioxidant, anti-inflammatory, antidiabetic, antimicrobial, anticancer, lipid-lowering, and cardiovascular-disease-lowering activities of cinnamon have been described (Rao and Gan. 2014), nowadays emerging evidence (mainly *in vitro* and *in vivo* studies) about it anti-obesity effect is emerging (Sartorius et al. 2014, Soliman et al. 2012). In this regard, 500 mg of a commercial water-soluble cinnamon extract (Cinnulin PF®, equivalent to 10 g of whole cinnamon powder) during 12-weeks was effective in reducing body fat and increase lean mass by 0.7% and 1.1% respectively in 22 participants with prediabetes and the metabolic syndrome compared to the control group (Ziegenfuss et al. 2006). The relationship between the fasting blood sugar and obesity has been previously highlighted and a recent cross sectional study showed that in obese the values of fasting blood sugar were significantly increased in obese persons, indicating the subjects are prone to develop cardiovascular & metabolic diseases (Akter et al. 2017). In this regard, Mang et al. (2006) demonstrated that 3 g of cinnamon powder per day for 4 months consumed by 79 patients with T2DM reduced fasting plasma glucose level more than 10% without improving the lipid profile (Mang et al. 2006). However, apart from showing a higher significant reduction in fasting serum glucose (18–29%), these earlier studies have also demonstrated a significant reduction in TG (23–30%), LDL-C (7–27%) and TC (12–26%) in 60 volunteers with T2DM who consumed 1, 3, or 6 g of cinnamon per day during 60 days (Khan et al. 2003). A more recent study supports a moderate effect in improving fasting blood glucose, HbA1c, TG, weight, BMI and body fat mass in 44 T2DM patients when 3 g cinnamon/day for 8-weeks were consumed (Vafa et al. 2012).

Cocoa beans and cocoa-based products are recognized as a good source of phenolic compounds. In fact, total phenolic content in cocoa beans suppose 6–8% of dry weight (Andres-Lacueva et al. 2008). Many attempts to evaluate the anti-obesity effect of cocoa and dark chocolate have been made in the last years. One of these researches includes the cross-sectional study carried out to investigate the effect of chocolate intake on BMI of 1017 subject (Golomb et al. 2012). This study concluded that adults who consumed chocolate frequently had lower BMI in comparison who those who consumed less often. Interestingly, they did not find any relationship between the quantification of chocolate consumed and BMI. Contrarily, Nogueira et al. (2012) did not find any change in anthropometric parameters, percentage body fat or lipid profile in 22 stage 1 hypertensive volunteers who consumed 50 g of chocolate (70% cocoa)/day (2135 mg polyphenols) for 4 weeks (Nogueira et al. 2012). Other possible mechanism of action related to dark chocolate obesity-management is the appetite suppression. In this regard, the intake of 100 g of dark chocolate decreased significantly the food and energy intake by 8% in 16 participants who consume it 2 h before serving an *ad libitum* meal compared to milk chocolate (Sørensen and Astrup. 2011). Massolt *et al.* (2010) also found appetite suppression after the consuming or smelling of dark chocolate in 12 women (Massolt et al. 2010). However, no changes in the blood satiety hormone levels cholecystokinin, ghrelin and glucagon-like peptide-1 compared to the control group were found. These high variability and the borderline positive effects do not allow establishing a real positive effect of cocoa-derived products in obesity management.

A commercial extract made up of a citrus polyphenolic extract of red orange, grapefruit and orange with ~90% of polyphenols, ~20% of flavanones and between 1 and 3% of natural caffeine was also reported to reduce waist and hip circumference and abdominal fat from overweight volunteers (Dallas et al. 2014). However, that study failed to study the target phenolic compounds responsible of its bioactivity.

5. Future prospect

Recent studies have shown that brown adipose tissue (BAT) is a promising target to treat human obesity and related metabolic disorders including diabetes mellitus (Saito et al. 2016). Despite the controversial about the existence of functional BAT in adults' humans (Cypess and Kahn. 2010, Trayhurn. 2017), a number of studies newly aimed to investigate the mechanism of action of polyphenols in obesity in BAT. Concretely, catechins from green tea or capsainoids from red pepper have been proposed as bioactive compounds which activate BAT *in vivo* increasing energy expenditure (Kawabata et al. 2006, Nomura et al. 2008, Ono et al. 2011). Moreover, oleuropein and oleuropein derivatives enhance thermogenesis by increasing noradrenaline and adrenaline secretion in brown adipose tissue in rats (Oi-Kano et al. 2008). Nevertheless, the extrapolation of these results to humans is a matter of concern and further studies are necessaries to demonstrate the implication of phenolic compounds in BAT activation. Moreover, factors, such as ethnicity, genetics and lifestyles, also need to be taken into account in designing clinical trials due to the heterogeneity in individual responses to nutrients due to genetic factors (Wang et al. 2014). To minimize these effects, dietary biomarkers are emerging as a promising tool for a better understanding of the metabolic effects of bioactive compounds in the body (Scalbert et al. 2009).

Concluding remarks

According to the European clinical practice guidelines (Tsigos et al. 2008), the treatment of obesity should be based on good clinical care and evidence-based interventions. Much evidence, both, *in vitro* and in animals models has been accumulated regarding the effect between phenolic compounds and their

anti-obesity effects. They are useful for a first screening of active plant extracts. However, unrealistic *in vivo* and preclinical assays, which cannot be later confirmed in humans, make difficult the advance in the anti-obesity effect of phenolic compounds. Moreover, limited human studies together with their inconsistence about the anti-obesity impact of polyphenols, makes necessary to generate more evidence in order to establish dietary recommendations for preventing obesity and obesity-related diseases. Furthermore, not enough set of well-designed trials support the anti-obesity effect of phenolic compounds-based products, so, more efforts and longer intervention trials are necessaries to confirm or complete the results already published. The standardization of the extracts seems to be also a requirement, not only to understand some of the contradictory results shown in aforementioned clinical studies but also to establish the active molecules and their effective doses.

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