Causes and solutions to "globesity": The new fa(s)t alarming global epidemic

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ABSTRACT

Diverse groups of factors are leading to increased weight gain and obesity, such as certain genetic phenotypes, neuroendocrine disturbances, the administration of some drugs, behavioral, social and environmental factors. The progressively escalating rates of overweight and obesity worldwide have led to an introduction of a new term "globesity". Excessive accumulation of body fat and especially of visceral adipose tissue is the main predisposing factor for the development of metabolic syndrome and other obesity related co-morbidities. At the present moment only few pharmacotherapeuticals are used for long-term treatment of obesity acting on narrow target spectra, *e.g.* pancreatic and gastric lipase inhibition, acting as adrenomimetics or activating the satiety centers in hypothalamus. Plant-based medications that accelerate weight loss, proved to be safe, effective and widely available, would be a preferable alternative for anti-obesity treatments. As plant extracts are multi-component systems they could also act by more than one mechanism, including decreased lipid absorption, decreased energy intake, increased energy expenditure, decreased pre-adipocyte differentiation and proliferation, decreased lipogenesis and increased lipolysis.

The current review gives a summary of the risk factors for obesity development and its characteristics consequences. Current treatment options, combining lifestyle changes and conventional treatment with commercial anti-obesity drugs have been described as well. Special emphasis on *in vitro*, *in vivo* and human studies, of potential medicinal plant extracts and phytochemicals, such as polyphenols, terpenoids, alkaloids, saponins, able to modulate the molecular pathways and gene/protein expressions related to obesity, have been highlighted.

1. Introduction

The number of people out of normal body weight range is constantly growing worldwide, indicating overweight and obesity as global concerns with expanding distribution. In 2016, more than 1.9 billion people, over 18 years, have been defined as overweight and above 0.65 billion of them as obese (NCD Risk Factor Collaboration, 2017). The worldwide prevalence of obesity expanded about three times within last ca. 40 years (between 1975 and 2016), defining obesity as global epidemics, hence introducing the term "globesity" (WHO, 2017).

The view of obesity as an imbalance between calories consumed and energy expended is nowadays rather oversimplified, since its multiplex etiology (González-Muniesa et al., 2017), comprising diverse groups of risk factors, such as certain genetic phenotypes [mutation in the leptin gene, fat mass and obesity associated (FTO) gene, melanocortin 4 receptor (MC4R) gene, etc.], neuroendocrine disturbances (hypothyroidism, hypogonadism, Cushing disease, etc.), behavioral factors (excessive consumption of "fast food" products, alcohol misuse), environmental factors (urbanization and pollution), epigenetic changes (Cheng et al., 2018) and some classes of obesogenic drugs (antidepressants, antiepileptics or antipsychotics) (Ghosh and Bouchard, 2017; Karam and McFarlane, 2007).

Obesity could be defined as a multifactorial disease characterized by excess adipose biomass (hypertrophy) and adipose tissue expansion (hyperplasia; Wang et al., 2014a,2014b), associated with co-morbid metabolic and chronic diseases, including low-grade inflammation, metabolic syndrome (MetS) (González-Muniesa et al., 2017), type 2 diabetes, elevated blood glucose, insulin resistance (Sompong et al.,
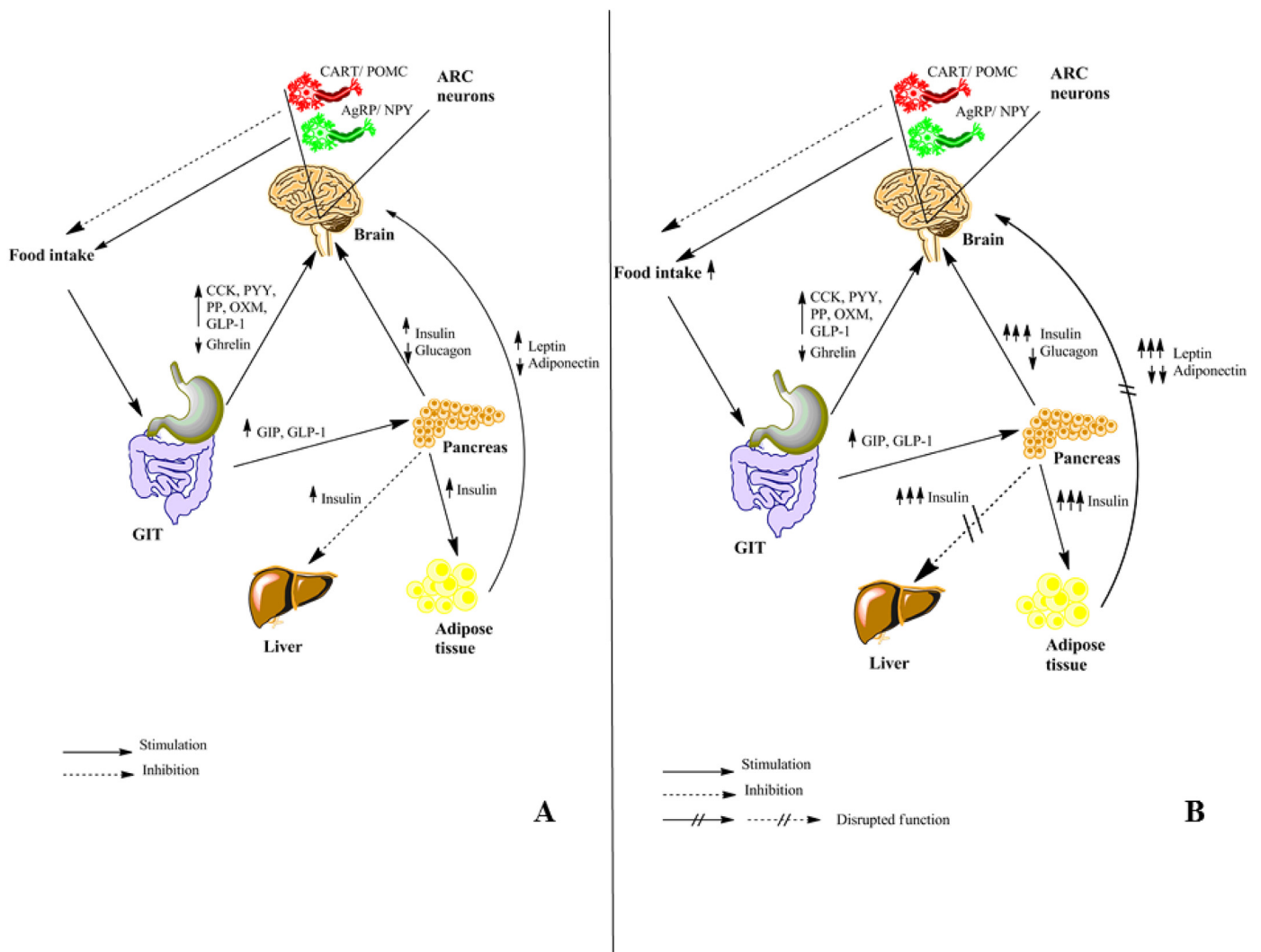
Fig. 1. Metabolic homeostatic system. (A) Healthy lean individual – after feeding the endocrine cells in the gut increase their secretion of satiety hormones (CCK, PYY, PP, OXM, GLP-1, GIP) and decrease that of the hunger signal ghrelin to inform the brain for the established energy balance. Subsequently, the absorbed nutrients from the consumed meal are sensed from the pancreatic cells and the insulin production is increased whereas the glucagon levels decreased. The GLP-1 and GIP produced from the gut act as incretins to further stimulate the pancreatic insulin production. The increased insulin inhibits the endogenic glucose production in the liver, increase the glucose utilization in the adipose tissue and sends signal to the brain when the glucose levels after meal are normalized. In the adipose tissue the excess glucose is transformed and stored as fat. The adipocytes increase their secretion of leptin and decrease that of adiponectin to indicate the brain for the raised levels of adiposity. In the ARC of the hypothalamus the leptin activates either the CART/POMC neurons to inhibit feeding or the AgRP/NPY to stimulate the appetite. This regulation is depending of the levels of leptin as well as the sensitivity of its receptors and also from the insulin signaling; (B) Obese individual – when an excess of nutrients is present for prolonged periods of time the body energy homeostasis is disturbed. The gut sends signals to the brain for satiety and stimulates the pancreas to increase its insulin production. The hyperinsulinemia which is characteristic for obesity aims to compensate the glucose overload. However, the insulin receptors in the different tissues decrease their sensitivity or even develop resistance to insulin. The consequences are disregulation in the gluconeogenesis in the liver, systemic hyperglycemia, increased fat storage in the adipocytes and subsequent hyperleptinemia. When the state of obesity is further aggravated leptin resistance is also developed in addition to the IR and the signaling of the ARC neurons is disturbed.

2016), cardiovascular diseases, hypertension, dyslipidemia, polycystic ovary syndrome (Hosseinkhani et al., 2018) and carcinogenesis (*e.g.* breast, colon, pancreas, kidney, esophagus, liver and prostate cancer; Wyatt et al., 2015). Social isolation, low self-esteem and chronic stress also correlate to obesity (Chaves Filho et al., 2018).

The current strategies for management of obesity and obesity-related disorders are classified in three main categories: lifestyle changes, pharmacological therapy and bariatric surgery (Haslam, 2016). Diet with caloric restrictions and increase in the daily physical activity are the first-line measures for obesity, but require period of months to get the first significant results. Addition of anti-obesity drugs to the lifestyle interventions increase the weight loss with about 3–5% compared to diet or exercises alone (Srivastava and Apovian, 2018). However, the pharmacotherapy of obesity is comprised from very short list of approved drugs associated with certain safety considerations and great variability between individuals in their response to the treatment (Manning et al., 2014; Srivastava and Apovian, 2018).

The natural multi therapy approaches have been accepted worldwide and during the recent decades a renewed interest in utilization of numerous plant extracts and individual phytochemicals or combinations of them as potent weight reducing agents with beneficial effect over obesity disorders has been observed. Evaluating plants from the traditional herbal medicinal systems supported with science-based evidences for their efficacy, safety profile, and mechanisms of activities is a required process to elucidate new potent bioactive leads (de Freitas Junior and de Almeida, 2017; Martel et al., 2017; Yun, 2010).

In the present review some of the advances in the pathophysiological mechanisms involved in obesity, as well as, novel therapeutic targets are discussed. Additionally, recent data on plant-based extracts and isolated compounds with anti-obesity potential are considered, explicating the most promising mechanisms to manage obesity from the perspective of *in vitro, in vivo*, and clinical studies.

2. Regulation of energy homeostasis

The energy balance in the human body is regulated in the brain as an integrating center for the information from peripheral receptors, hormones, mediators and neurotransmitters as signals for hunger and satiety. The co-ordination of these signals is proposed to involve at least two parallel systems: the metabolic homeostatic system and the brain reward system (Kenny, 2011).

2.1. Metabolic homeostatic system

The homeostatic system participate in the complex regulation of hunger, satiety and adiposity levels through hormones such as leptin, ghrelin, insulin and glucagon, intermediating the communication between the gut and the brain structures, especially in the hypothalamic area, to induce or suppress food consumption and provide proper energy balance (Gao and Horvath, 2007).

Initiation of feeding activates the enteric nervous system *via* either parasympathetic stimulation or distention of the stomach and leads to secretion of digestive enzymes. Enzymes such as lipases, proteases, glucosidases and amylase are produced by different exocrine glands in the gut to control the breakdown and absorption of nutrients from the ingested food. After meal variety of satiety signals are produced to indicate the appetite control centers in the brain, located within the nucleus of the solitary tact and the hypothalamus, for the establishment of energy balance (Fig. 1A; Blouet and Schwartz, 2012).

Chronic overfeeding and constant consumption of high-fat diet (HFD) result in an excessive supply of nutrients to the metabolic organs and is temporally related to periods of weight gain, and associated with obesity, disrupted insulin and leptin signaling and impaired energy homeostasis (Fig. 1B; Morrison et al., 2009).

2.2. Brain reward system

In addition to the homeostatic regulation, the brain reward systems also contributes to maintaining balanced energy levels by influencing the feeding behavior. Whereas the metabolic homeostasis is controlled predominantly by hypothalamic and brainstem circuits, the hedonic value of the consumed food is evaluated in the mesolimbic and cortical brain areas. Multiple pathways interplay in this process such as dopaminergic, noradrenergic, cholinergic, serotonergic, and histaminergic, as well as the endocannabinoid (eCB) system and several neuropeptides such as gamma-amino-butyric acid (GABA) and glutamate (Ahima and Antwi, 2008; Kenny, 2011).

The dopaminergic neurons of the ventral tegmental area send upstream signals to the nucleus accumbens, the striatum and the prefrontal cortex, playing central role in the regulation of reward motivated behavior. As part of the mesolimbic system the orbitofrontal cortex and the amygdala also contribute in the processing of hedonic value of the food and the reward-related learning (Alonso-Alonso et al., 2015; Hall et al., 2014).

Recent studies report that common pathways are activated in response to drugs with addictive potential (*e.g.* cocaine) and food stimuli, arising the need for more detailed understanding of the activation of hedonic hunger and food addiction (Alonso-Alonso et al., 2015). However, strategies how to modulate the brain reward signaling to prevent obesity development remain unclear (Burger and Berner, 2014; Kenny, 2011). The modern imaging techniques, such as functional magnetic resonance and positron emission tomography, data from bariatric surgery follow-up studies and animal models could provide valuable missing interconnections between the homeostatic and reward systems regulating the energy balance and food-driven behavior (Burger and Berner, 2014).

3. Risk factors for obesity development

The process from gaining extra weight to developing pathologic obesity is usually long and polygenic. Several groups of risk factors influence body weight gain and interplay in the development of obesity such as excessive food consumption, low levels of physical activity, certain genetic phenotypes, disturbed neuroendocrine regulation, societal and environmental factors, epigenetic changes and iatrogenic factors (Cheng et al., 2018; González-Muniesa et al., 2017; Hennig et al., 2018; Karam and McFarlane, 2007).

3.1. Lack of energy balance

The most common risk factors for gaining weight are the overconsumption of energy-dense foods and the sedentary lifestyle (González-Muniesa et al., 2017). When there is an excess of energy from food that is not needed, it is hence stored in the organism mainly as fat in the adipose tissue. However, there are remarkable differences in the way people accumulate body fat, which is one of the complexities to study risk factors in obesity. An obvious example of such heterogeneity is the variation in body configuration and in regional accumulation of body fat at any given adiposity level (González-Muniesa et al., 2017). For example, two people from the same gender, with the same body weight and height could look completely different, depending of their body composition (*e.g.* levels of fat and muscle tissue). Furthermore, the differences in fat deposition patterns have been described in monozygotic twins with identical genetic background, suggesting important role of the nutrition and epigenetic interactions in obesity development. Therefore, maintaining a healthy lifestyle involves more of a focus on the quality of foods eaten and the overall metabolic balance than on kilograms or calories alone (Cheng et al., 2018; Hennig et al., 2018).

3.2. Genetic factors

Few decades ago the understanding of genetic determinants of body weight regulation in humans was relying on the study of rodent models of obesity. Monogenic deficiencies of appetite-regulating hormones or their receptors such as leptin, leptin receptor and MC4R are examples that accounts for a minor proportion of severe young-onset forms of obesity (Ghosh and Bouchard, 2017; Spiegelman and Flier, 2001).

The first single polymorphism that has been found to strongly correlate with elevation in the BMI and hyperphagia was the FTO gene (Fall and Ingelsson, 2014). Congenital genetic disorders manifested with severe obesity are Alstrom-Hallgren, Bardet-Biedl, Beckwith-Wiedeman, Carpenter, Cohen and Prader-Willi syndromes, the latter being one of the most common syndromic types of childhood obesity (Rahilly, 2009).

The advent of large-scale genotyping allowed for a more comprehensive, unbiased and data-driven approach in the search for causal genetic mechanisms underlying obesity which was extensively presented in the review papers on genome-wide association studies of obesity, MetS and BMI (Fall and Ingelsson, 2014; Ghosh and Bouchard, 2017; Locke et al., 2015).

3.3. Neuroendocrine factors

Dysfunctions in the neuroendocrine system such as hypothyroidism, Cushing disease, somatotropin deficiency, hypothalamic damage, hypogonadism, pseudohypoparathyroidism and insulinoma are commonly associated with increased risk of obesity development (Karam and McFarlane, 2007).

For example, decrease in the thyroid hormones drop the rates of the resting metabolism, thermogenesis and cellular respiration processes (Karam and McFarlane, 2007). The injury of the hypothalamus could also lead to rapid weight gain since it plays a key role in integrating information regarding the metabolic homeostasis (Williams et al., 2000). Excessive levels of the endogenous corticoids which are typical in the Cushing syndrome generate specific central fat accumulation pattern in the abdominal area, the face, the neck, the humps and the upper arms without affecting the extremities (Karam and McFarlane, 2007).

3.4. Drug-induced obesity

Several classes of drugs are known to induce obesity as side-effect of their use, such as the antipsychotics, antiepileptics, antidepressants, corticosteroids and some of the antidiabetics (Karam and McFarlane, 2007; Verhaegen and Van Gaal, 2017).

The long-term systemic administration of corticosteroids promotes weight gain by multiple mechanisms: activation of the hypothalamic-pituitary-adrenal (HPA) axis, the eCB system, modulation of the AMP-activated proteinkinase (AMPK) activity in the hypothalamus and thus stimulating the appetite, decrease in the energy expenditure and increase in the fat accumulation in the liver. In addition, the corticosteroids induce glucose intolerance in a dose-dependent manner by inducing hepatic and extrahepatic insulin resistance (Verhaegen and Van Gaal, 2017).

Antipsychotics, antiepileptics and antidepressants as psychoactive drugs modulate multiple systems in the brain (dopaminergic, noradrenergic, serotonergic, and histaminergic neurotransmission, GABA), thus affecting through diverse mechanisms satiety and energy

homeostasis, leading to weight gain as a side effect (Schwartz et al., 2004).

Insulin, sulfonylureas, and thiazolidinediones (TZDs) are among the antidiabetic agents associated with substantial weight gain, due to increased appetite and fat accumulation which result from the adverse issues with hypoglycemia or poor glycemic control. Insulin itself further increase the risk of gaining weight because of its anabolic action (Verhaegen and Van Gaal, 2017).

3.5. Behavioral, societal and environmental factors

Except from sustained positive energy balance, the attitude towards feeding and other behavioral and socioeconomic factors could influence excessive weight gain (Burger and Berner, 2014; Karam and McFarlane, 2007).

The societal and environmental factors favoring obesity development include the easy access and commercialization of processed food with high-caloric values, the increasingly sedentary forms of work, lack of pedestrian zones for walking and increase in the use of transportation, due to the need of saving time and crossing long distances in the big urbanized cities (Lopez and Hynes, 2006). In addition, the lack of supportive policies in sectors such as health, agriculture, ecology, urban planning, food processing, distribution, marketing, sports and education also contribute to the complex etiology of obesity (González-Muniesa et al., 2017). Environmental pollutants to which people are exposed daily substantially increase the risk of epigenetic changes and further aggravate the metabolic complications of obesity and type 2 diabetes (Cheng et al., 2018; Hennig et al., 2018).

Ethnicity and family pattern feeding behavior play role in what the person think is healthy body-weight. Even though the scientific data is controversial, bad habits such as alcohol abuse and smoking increase the long-term risk of obesity and metabolic disorders (Traversy and Chaput, 2015). Smokers tend to have relatively lower BMI, but increased risk for future metabolic complications compared to non-smokers. Moreover, smoking cessation has been linked to a 3–5 kg average weight gain (Karam and McFarlane, 2007).

4. Assessment parameters and epidemiology

Various assessment parameters are used to appropriately determine which of the people that are overweight or obese are at risk of serious consequences for health (Duren et al., 2008). The most easily applicable are the anthropometric measures, such as measuring the total body weight (BW), height, waist circumference (WC), hip circumference (HC) or calculating the BMI. In general, individuals with high BW typically have higher amounts of body fat (Wells and Fewtrell, 2006).

The BMI is the most frequently used indicator for scoring the degree of obesity that correlates weight and height, having as main advantage the possibility to be interpreted in correlation with wide national reference data of the levels of adiposity, morbidity and mortality in adults (Lo et al., 2016). The calculation of the BMI is represented by the following simple equation: $BMI = BW (kg)/Height^2 (m)$. According to the classification of the World Health Organization (WHO) for obesity a person is within the normal range if the BMI is between 18.5 kg/m^2 and 24.9 kg/m^2 (Fig. 2). However, BMI alone cannot provide information about the body composition and respective contribution of fat free mass (FFM) or fat mass (FM) to body weight which suggest the use of additional indicators for central adiposity in overweight and obese people. The WC is such indicator of the visceral adipose tissue (VAT), but it also
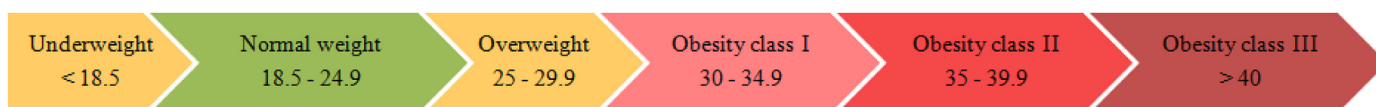

| Underweight | Normal weight | Overweight | Obesity class I | Obesity class II | Obesity class III |
| < 18.5 | 18.5 - 24.9 | 25 - 29.9 | 30 - 34.9 | 35 - 39.9 | > 40 |

Fig. 2. The BMI (kg/m^2) categories according to the WHO data.

includes subcutaneous abdominal fat which decrease its sensitivity to predict obesity-related complications (Wells and Fewtrell, 2006).

Waist to hip ratio (WHR), waist to height ratio (WHtR), conicity index and abdominal volume index are indexes that have been developed to better discriminate those at higher risk for developing metabolic complications due to central obesity. However, there is insufficient data on these measures (*e.g.* WHtR), to suggest giving any priority at present, thus, due to the relative ease of obtaining, WC and the BMI are the most widely used parameters to predict the risk of obesity consequences (Motamed et al., 2015).

To discriminate the levels of adipose tissue out of the total body composition more precise techniques could be used such as bioelectric impedance analysis, dual energy X-ray absorptiometry, densitometry, magnetic resonance imaging and computed tomography, but their use is mainly restricted to laboratory settings (González-Muniesa et al., 2017).

Data from epidemiological studies showed that between 1980 and 2008, the global age-standardized mean for BMI increased by 0.4 kg/m^2 (in men) to 0.5 kg/m^2 (in women) per decade (Finucane et al., 2011). The portion of adults with a BMI higher than 25 kg/m^2 increased with about 8% between 1980 and 2013. By 2030, estimates forecast that 57.8% (3.3 billion people) of the world adult population will have a BMI of 25 kg/m^2 or higher (Finkelstein et al., 2012).

Most of the world's population is threatened to become overweight and obesity than underweight. Furthermore, obesity among children is enormously increasing its numbers with over 107 million children found to be obese in 2015 which predicts future aggravation of the globesity problem (Global Burden of Disease, 2017).

5. Consequences of obesity

Overfeeding and obesity lead to pathophysiological changes that disrupt the functions of various organs and tissues. Subsequently these metabolic complications increase the risk of development serious health problems in obese individuals (González-Muniesa et al., 2017).

5.1. Common comorbidities

Obesity and especially excessive accumulation of intra-abdominal fat are the main predisposing factors for development of MetS, which is characterized as complex pathology clustering of several metabolic disturbances (Fall and Ingelsson, 2014). The most recent harmonized definition from 2009 states as inclusion criteria for MetS the presence of at least 3 of the following 5 risk factors: (1) enlarged WC with population-specific and country-specific criteria (for example, in the Western World WC ≥ 94 cm in men and WC ≥ 80 cm in women); (2) hypertriglyceridaemia ≥ 150 mg/dL or on triglyceride-lowering medication; (3) low levels of high-density lipoprotein cholesterol (HDL-C): < 40 mg/dL for men and < 50 mg/dL for women; (4) elevated blood pressure: systolic blood pressure of ≥ 130 mmHg, diastolic blood pressure of ≥ 85 mmHg or on antihypertensives; (5) increased glucose levels: fasting glucose levels of ≥ 100 mg/dL or on antidiabetics (Silva et al., 2013).

In addition, to the increased risk of developing features of the MetS, other common to obesity co-morbidities are endocrine disorders (such as type 2 diabetes and polycystic ovaries syndrome), respiratory problems (for example, obstructive sleep apnea), cardiovascular diseases (such as atherosclerosis and heart attack), mood-disorders (such as depression and anxiety), and certain types of cancers (for example, pancreatic, liver and kidney cancer) (González-Muniesa et al., 2017).

5.2. Chronic low-grade inflammation in obesity

Recently, increasing number of studies associate obesity with a state of systemic low-grade chronic inflammation, which may be the precipitating factor for many of its associated complications (Chawla et al., 2012; Winer et al., 2016).

In the gut where all the food is processed the disturbances accompanying obesity are of great importance and is hard to differentiate weather they are causes or consequences for this pathologic condition. Link between diet-induced obesity and dysbiosis in the gastro-intestinal tract is suggested both in experimental and clinical studies (Luck et al., 2015; Nguyen et al., 2017; Winer et al., 2016). Winer et al. (2016) provide excellent comprehensive review of the interconnection between the intestinal immune system, the gut microbiota and the chronic inflammation displayed in different tissues in obesity (Winer et al., 2016). Feeding predominantly with the HFD rich of saturated fatty acids and cholesterol is proposed to alter the composition of the gut microbiota, leading to dysbiosis. The dysbiosis favors the reduction of commensal bacterial species that produce anti-inflammatory metabolites, such as short-chain fatty acids, which, in turn, promotes inflammatory immune changes within the intestines. The intestinal epithelial cells (IECs) and the gut resident immune cells secrete pro-inflammatory mediators such as interferon γ (IFNγ) and interleukin-1β (IL-1β) that weaken the intestinal barrier, increase the intestinal permeability to luminal microbial or dietary components and lead to a state of a low-grade chronic gut inflammation. Subsequently, the leaked luminal microbial and dietary components such as lipopolysaccharide (LPS) enter the systemic circulation to induce inflammation into multiple organs and tissues – pancreas, liver, muscle and adipose tissues (Winer et al., 2016).

The pancreatic function in obesity is disturbed not only due to increased lipid accumulation, but also to altered incretins' signaling and insulin secretion from the β-cells. Moreover, obese compared to lean individuals have greater probability to develop acute pancreatitis or pancreatic cancer (Gregor and Hotamisligil, 2011). The inappropriate insulin secretion decrease the insulin sensitivity in other tissues and organs, especially the liver where it regulates the hepatic gluconeogenesis (Luck et al., 2015).

The liver reacts to the increased glucose levels with development of IR. In addition to this state of glucotoxicity, the liver function is disturbed due to the excessive lipid accumulation which is defined as a state of lypotoxicity or liver steatosis (Jung et al., 2016b). In response to the overload with glucose and lipids the hepatocytes up-regulate their production of pro-inflammatory hepatokines such as fetuin A, selenoprotein P, leukocyte cell-derived chemotaxin 2 and chemerin (Jung et al., 2016b; Oh et al., 2017).

The muscle tissue was also recognized as an endocrine organ, which was comprehensively reviewed elsewhere (Ahima and Park, 2015; Li et al., 2017). Myokines such as irisin, IL-6, interleukin-15 (IL-15), insulin-like growth factor I (IGF-I), brain-derived neurotrophic factor (BDNF), and follistatin-related protein 1 (FSTL1) are involved in insulin signaling and energy metabolism (So et al., 2014). Furthermore, myokines are responsible to mediate the communication between the muscle and the adipose tissue, the liver, the brain, and other organs. In obesity the muscle tissue is characterized with decreased insulin sensitivity or even IR, and due to metabolic deregulation increase its production of the pro-inflammatory myostatin leading to myoatrophy (Ahima and Park, 2015). This state is further aggravated by the lack of muscle contractility in obese individuals leading to decrease in the levels of the anti-inflammatory "exercise-induced" myokines such as that of BDNF, leukemia inhibitory factor (LIF), irisin, fibroblast growth factor 21 (FGF-21), secreted protein acidic and rich in cysteine (SPARC; Oh et al., 2017).

In the adipose tissue as main fat storage the most abundant changes in obesity occur. The adipocytes are not only responsible for fat metabolism and accumulation, but also possess secretor functions of autocrine, paracrine and endocrine character (Rodríguez et al., 2015). Excessive weight gain leads to hyperplasia and/or hypertrophy of the adipocytes, altered adipokines secretion, decreased insulin sensitivity, shift in the profile of the immune cells resident for the fat tissue thus leading to low-grade chronic inflammation (Mathis, 2013).
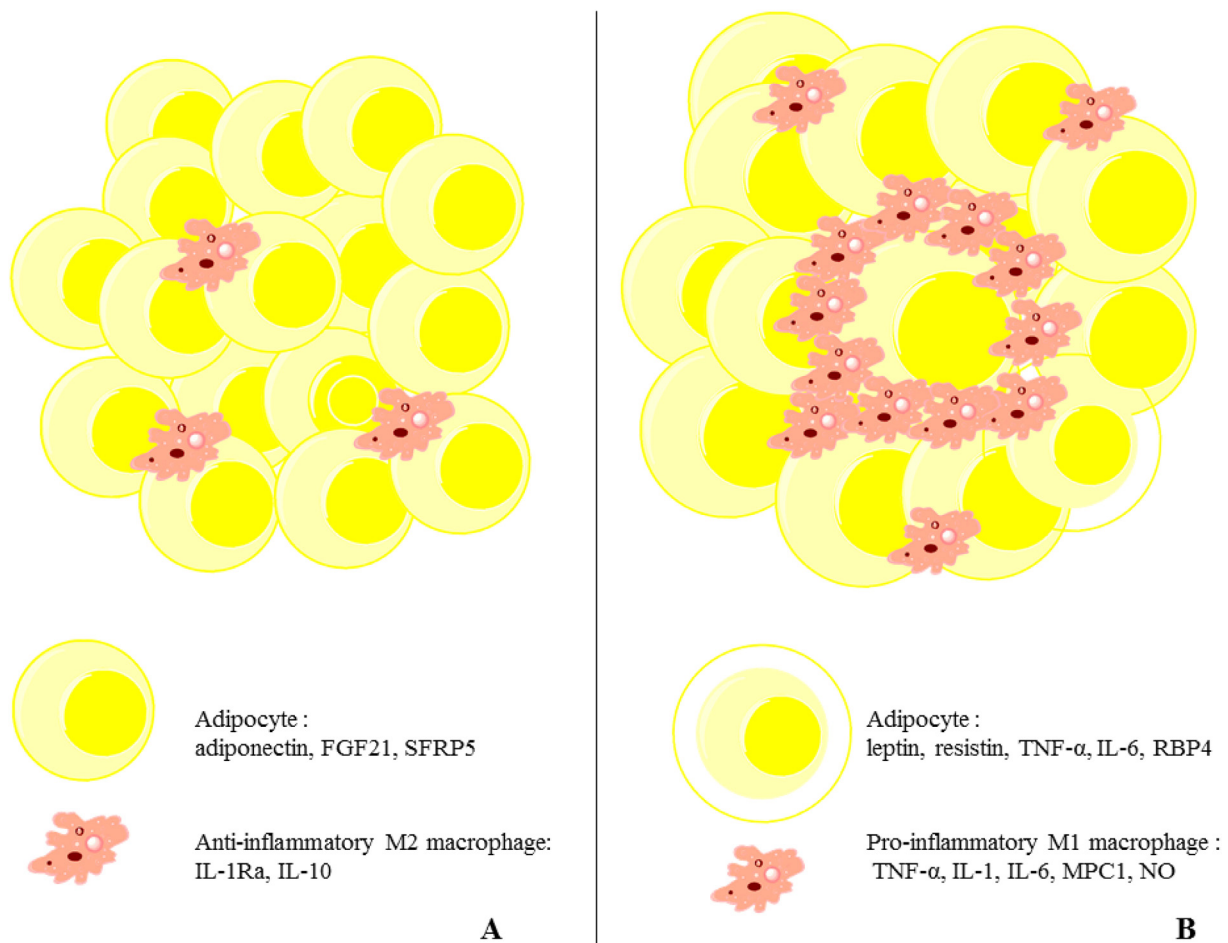
Fig. 3. Adipocytes and the resident macrophages in the adipose tissue. (A) Healthy lean individual – the adipose tissue secretes mainly anti-inflammatory adipokines (adiponectin, FGF21, SFRP5) and the predominant type of resident macrophages are the anti-inflammatory type 2 (M2) which secrete cytokines such as IL-1Ra, IL-10; (B) Obese individual – the hypertrophied adipocytes have increased production of pro-inflammatory adipokines (leptin, resistin, TNF-α, IL-6, RBP4). The resident macrophages have shifted mainly towards type 1 (M1) and their cytokines profile is pro-inflammatory (TNF-α, IL-1, IL-6, MCP1, NO). When an adipocyte is saturated it becomes apoptotic and the M1 macrophages form a "crown-like" structure around it as another hallmark of adipose tissue chronic inflammation.

Two types of adipose tissue are distinguished white adipose tissue (WAT) which is the active endocrine organ that dynamically stores fat and brown adipose tissue (BAT) that primarily converts energy into heat upon β-adrenergic stimulation or cold exposure, a process known as thermogenesis. Recently the presence of third type adipocytes described as brown-likecells also termed beige or brite (brown-in-white) have been revealed, which under basal conditions are not thermogenically active as white adipocytes, but upon β-adrenergic stimulation induced by cold exposure or exercise show thermogenic properties such as the brown fat cells (Wu et al., 2012).

In environment of excess nutrients, if the subcutaneous WAT handles the energy excess by causing hyperplasia, such properly expanding adipose tissue will then act as a "metabolic sink", protecting lean tissues (for example, the heart, liver, pancreas and the kidneys) against harmful ectopic fat deposition. Conversely, if hyperplasia do not occur, the stored triglycerides will contribute to adipocyte hypertrophy until these large adipocytes become saturated and are no longer able to expand. This is leading to increased release of pro-inflammatory and reduction of anti-inflammatory adipokines by the hypertrophied adipocytes and/or their rupture and macrophage invasion (Fig. 3; Gupta, 2014).

Nowadays, it is well known that in the adipose tissue resident macrophages are classified according to their cell surface markers and secretory profiles as type 1 (M1) and type 2 macrophages (M2). M1 macrophages play a key role against bacterial and viral infections, being activated by IFNγ and LPS, and secrete pro-inflammatory cytokines. By contrast, M2 macrophages are associated with anti-inflammatory responses and are induced by exposure to interleukin 14 (IL-14) and interleukin 13 (IL-13). While in healthy lean individual there are predominantly anti-inflammatory M2 over M1 macrophages, obesity is associated with a switch towards the M1 pro-inflammatory phenotype (Chawla et al., 2012).

Additionally to the resident macrophages, other immune cells of the adaptive (B and T lymphocytes) and innate (dendritic cells, mast cells or eosinophils) system further aggravates the adipose tissue inflammation and contribute to the onset of obesity-associated comorbidities (Lee and Lee, 2014; Rodríguez et al., 2015). The activated immune cells sustain the chronic production of pro-inflammatory adipokines, leading to decreased insulin sensitivity and form vicious circle of the chronic systemic inflammation in obesity (González-Muniesa et al., 2017).

6. Current treatment options

The established strategies for obesity management fall in three categories: lifestyle interventions, pharmacotherapy and bariatric surgery.

6.1. Lifestyle modifications

Lifestyle interventions have been an important part of weight loss management for more than a quarter of a century. Diet modifications and increase in physical activity are the first measures to be recommended and although having good long-term efficacy the first results are visible after months or up to a year (mean weight loss of 3 kg for 12 months). A meta-analysis indicated that physical activity results in additional 1–1.5 kg lost weight over 12 months than a dietary intervention alone (Wu et al., 2009).

A restriction of 500 kcal/day or 30% from the average individual daily intake, or a diet with 1200 kcal/day for women and 1500 kcal/day for men is generally recommended for weight loss (González-Muniesa et al., 2017). The ideal healthy diet is the one that comprise of balance of the macronutrients (proteins, carbohydrates and lipids), as well as, the micronutrients and vitamins needed for the organism. Some food components are well known to be beneficial for human health such as green-leaf vegetables, fruits rich in fibers, seeds, nuts and fish rich in essential fatty acids (Omega 3 and 6), meat and dairy products rich in proteins (Hennig et al., 2018; Lucan and DiNicolantonio, 2015).

However, many people struggle to comply with restricted calories diet for long period of time and they often re-gain the lost weight very fast after stopping with the weight loss regimen (González-Muniesa et al., 2017). When interventions to restore the energy balance are initiated the individual variation in weight loss response is striking, and therefore there is need to reveal the mechanisms responsible for the underlying differences in compensatory adaptive response to caloric restrictions, food rewards, and re-establishment of metabolic homeostasis (Hall et al., 2012).

6.2. Pharmacotherapy

From historical perspective great variety of drugs have been used for weight loss, but because of their side effects such as rebound weight gain, sleep disturbances, anxiety, depression, anorexia, serious cardiovascular incidents and risk for tolerance and abuse many them were of withdrawn from the market (Fenske et al., 2011). For example, in the last few decades the European Medicines Agency (EMA) discontinued the use of phentermine, mazindol and diethylpropion (in 2000), rimonabant (in 2008) and sibutramine (in 2010; Fujioka, 2015).

Currently approved anti-obesity medicines can be classified into two broad categories: peripherally acting agents that inhibit food absorption in the gut and centrally acting agents that inhibit food intake by acting on the brain's satiety, hunger and reward centers. In the USA, as for 2017, nine therapeutic options are approved by the Food and Drugs Administration (FDA), whereas due to certain safety considerations the EMA have currently approved only three of them (Table 1).

Orlistat is an anti-obesity drug that acts peripherally on reducing the efficiency of digestion by inhibiting pancreatic and gastric lipases and decrease the amount of fats absorption from food. The pancreatic lipase hydrolyzes 50–70% of the consumed fats to monoacylglycerols and fatty acids and aids their subsequent absorption (Seyedan et al., 2015). Orlistat reduces the intestinal fat absorption with around one third without affecting the appetite (Alonso-Castro et al., 2015; Jaradat et al., 2017). It is the only drug for weight loss that could be used without prescription for prolonged period and thus is the most widely used in obesity management. The most common side effects from its administration are abdominal pain and diarrhoea. In experimental studies for new potential pancreatic lipase inhibitors orlistat is usually used as reference substance (Jaradat et al., 2017).

Another peripherally acting agent is liraglutide which is human analogue of GLP-1 produced by recombinant DNA technology in *Saccharomyces cerevisiae* with anorexigenic effect, initially approved in the therapy of type 2 diabetes. Except from acting by enhancing the insulin production after meal, it also induces satiety through not yet clarified mechanisms. However, novel GLP-1 agonists are under study

in order to lower the chance of hypoglycemic complications and increase the weight reduction potential (Srivastava and Apovian, 2018; Zhou et al., 2017). The centrally acting drugs for obesity are mainly from the group of sympathomimetics that increase the noradrenalin and dopamine levels and inhibit hunger signals by activation of the adrenergic mediation. These drugs are structurally similar to amphetamines and also possess similar to their side effects such as dependence, tolerance and tachycardia (Fenske et al., 2011). Phenteramine and its analogues are not recommended for long-term administration as monotherapy for obesity (Srivastava and Apovian, 2018). Lorcaserin is another centrally acting anti-obesity agent approved by FDA acting as agonist for serotonin receptors subtype 2C ($5HT_{2C}R$), thus stimulating the satiety centers in the brain (Greenway et al., 2016). In the European Union lorcaserine was withdrawn from the market in 2013 due to safety considerations which defines the need for development of new safer serotonergic anti-obesity drugs (Voigt and Fink, 2015).

The concept of targeting multiple regulatory pathways of energy balance has become popular as a potentially safer and more efficient strategy for obesity treatment as monotherapies that selectively target one specific system in the brain rarely achieve greater efficacy than 5% weight loss (Manning et al., 2014). Phenteramine in combination with the antiepileptic drug topiramate is approved for prolonged use in obesity by the FDA showing grater efficacy of the combination than of phenteramine or topiramate alone (Aronne et al., 2013). Another combination used to modulate the brain reward and satiety systems is the opioid receptors' antagonist naltrexone and the dopamine and noradrenaline selective re-uptake inhibitor bupropion which is also approved for prolonged use and with overall good efficacy from the treatment (Srivastava and Apovian, 2018).

6.3. Bariatric surgery

Bariatric or weight loss surgical procedures generally aim to decrease the capacity of the stomach. Gastric bypass, sleeve gastrectomy, implantation of adjustable gastric band and biliopancreatic diversion are among the most commonly performed procedures in bariatrics. The gastric bypass which stands out as a gold standard in weight loss surgery is done by resecting part of the stomach and re-connecting the small intestine to a small stomach part left (Chang et al., 2014a,b).

Currently, this treatment option is considered only for patients with BMI over 40 kg/m^2 or over 35 kg/m^2 with one or more obesity-related co-morbidities, as being the most effective in terms of lost weight and maintenance of the results. Records of diabetic patients undergone bariatric surgery report decrease in the dose of insulin and oral antihyperglycemics used. Other additional benefits include reduced rates of hypertension, obstructive sleep apnea and improved lipid profile at 3–5 years post-surgery (Varban et al., 2017).

7. Emerging targets for treatment of obesity

In the last decade many novel regulators of energy metabolism that have improved the basic knowledge of the pathophysiology of obesity and highlighted potential targets for novel treatment options have been defined (Table 2). The anti-obesity effect of molecules targeting various neuropeptides or their receptors, different transcription factors, enzymes and proteins have been evaluated in numerous research papers (Ahima and Antwi, 2008; Fujioka, 2015; Girardet and Butler, 2014; Kajimura et al., 2015; Manning et al., 2014; Matzinger et al., 2017).

7.1. Neuropeptides and their receptors

Varieties of potential weight loss drugs have been designed to target the brain circuitsresponsible for the regulation of energy homeostasis and feeding behavior. However, it must be taken into account that most of the targeted pathways action is not restricted to only central mechanisms, but also could produce peripheral effects, both desired or

Table 1

Anti-obesity drugs currently approved by the European Medicine Agency (EMA) and the Food and Drug Administration (FDA).

Anti-obesity drug (available doses)	Treatment reccomendations	Efficacy (% of initial weight lost more than placebo-treated individuals)	Mechanism of action	Common side effects and serious adverse events	EMA	FDA	Reference
Peripherally acting							
Orlistat (60 mg, 120 mg)	120 mg three times per day orally for prolonged use	Average 3% after 1 year	Inhibits the pancreatic and gastric lipases and the hydrolysis of triglycerides in the gut	Gastrointestinal disturbances such as nausea, diarrhoea, abdominal pain, flatulence, rectal discharge; some reports for severe liver disorders	+	+	Jarl and Mark, 2004
Liraglutide (3 mg)	3 mg once per day subcutaneosly for prolonged use	Average 6% after 56 weeks	An agonist of GLP-1 leading to increased postprandial insulin secretion and inhibition of glucagon action	Gastrointestinal disturbances such as nausea, diarrhoea, abdominal pain, constipation and dyspepsia; nasopharyngitis; risk of severe hypoglycemia; acute pancreatitis	+	+	Mehta et al., 2017
Centrally acting							
Phentermine (8 mg, 15 mg, 30 mg)	15 mg once per day or up to 30 mg once per day orally for short-term use (recommended for up to 12 weeks)	Average 5% after 28 weeks	Sympathomimetic action similar to amphetamines that increase the release or inhibit the reuptake of the bioactive monoamines - mainly of noradrenaline and dopamine	CNS effects such as tolerance, dependence and withdrawal syndorme; cardio-vascular events such as tachycardia, paplitaions and hypertension; serious risk of primary pulmonary hypertension	-	+	Aronne et al., 2013
Diethylpropion (25 mg, 75 mg)	up to 75 mg once per day orally for short-term use	*	dopamine	hypertension	-	+	Srivastava and Apovian, 2018
Phendimetrazine (35 mg, 105 mg)	35 mg three times per day orally for short-term use	*			-	+	Srivastava and Apovian, 2018
Benzphetamine (25mg, 50 mg)	25 mg or 50 mg up to three times per day orally for short-term use	*			-	+	Srivastava and Apovian, 2018
Naltrexone/bupropion (8 mg/ 90 mg)	up to 32 mg/360 mg per day orally for prolonged use	Average 5% after 56 weeks	Opioid receptors' antagonist/antidepressant drug -inhibitor of the reuptake of dopamine and noradrenaline	For naltrexone - tolerance, dependence and withdrawal syndorme; suicidal toughts; activation of mania in patients with pschyatric disorders; for bupropion - increased risk of seizures; hepatotoxicity	+	+	Apovian et al., 2013
Phentermine/topiramate (3.75 mg/23 mg, 7,5 mg/46 mg, 11.25 mg/69 mg, 15 mg/ 92 mg)	up to 15 mg/92 mg per day orally for prolonged use	Average 8% after 56 weeks	Sympathomimetic drug/antiepilepthic drug acting on GABA-A receptors, voltage-gated ion channels, AMPA/kainate receptors and carbonic anhydrase isoenzymes	For phenteramine (as mentioned above); for topiramate - diarrhoea; nausea; paraesthesia; depression; suicidal toughts; teratogenity	-	+	Aronne et al., 2013; Gadde et al., 2011
Lorcaserin (10 mg)	10 mg once or two times per day orally for prolonged use	Average 3% after 1 year	Selective 5-HT$_{2C}$ agonist activating the satiety center in hyppothalamus	Paraesthesia and hypoaesthesia; memory impairment and amnesia; increased risk of hypoglycemia in patients with diabetes; low risk of primary pulmonary hypertension and cardiac valvular insufficiency	-	+	Apovian et al., 2016

+ Approved; - Not approved; * Similar to phenteramine or with few data from controlled trials evaluating its efficacy.

Table 2
Emerging targets for treatment of obesity.

Novel targets		Function in obesity	Reference
Neurpeptides and their receptors	MCs	MC4R is known to be crucial to the regulation of satiety signals. MC3R is also expressed in the CNS and is linked with energy homeostasis, but his function is not clearly elucidated yet	Shen et al., 2017
	NPY	NPY is thought to stimulate appetite by activation of the Y1 and Y5 receptors in the hypothalamic AgRP/NPY neurons. Antagonists at these receptors have been studied with the aim of blocking this orexigeniceffect	Yulyaningsih et al., 2011
	eCBs	The CB1 receptors mediate the metabolic actions of eCBs including increased feeding motivation and reduction in energy expenditure	Sharma et al., 2018
	NmU	NmU activate the AgRP/POMC neurons in ARC and neurons in PVN mediating anorectic effects	Kaisho et al., 2017
Transcription factors	PPARs	PPARs regulate the fatty acid storage and glucose metabolism	Gross et al., 2017
	C/EBPs	C/EBPs are known adipogenic transcription factors, crucial for the adipocyte development	Mueller, 2014
	SIRT	Activation of SIRT1 and potentially SIRT6 could be beneficial for the treatment of hyperglycemia in diabetes	Bae, 2017; Lee et al., 2014
	Nrf2	Activation of Nrf2 is suggested to play a role in insulin sensitivity, β-cell function and long-term complications of obesity and diabetes	Matzinger et al., 2017
Enzymes	AMPK	AMPK is activated under fasting conditions and causes increased fatty acid oxidation, glucose uptake and glycolysis, and the inhibition of fatty acid and glycogen synthesis	Manning et al., 2014
	PTP1B	The protein-tyrosine phosphatase 1B (PTP1B) takes part in the regulation of the tyrosine phosphorylation cascade integral to the insulin and leptin signaling pathways	Cho, 2013
	NNMT	NNMT is a cytosolic enzyme with a newly identified role in modulating cellular energy homeostasis	Neelakantan et al., 2018
Proteins	SOCS3	SOCS3 is a protein that inhibits the signal transduction process of leptin, thus its modulation could be beneficial in state of LR	Lubis et al., 2008; Manning et al., 2014
	Adiponectin	Adiponectin is an essential regulator of thermogenesis and thus is required for maintaining body temperature under cold exposure	Yamauchi et al., 2014
	UCP	UCP1 and UCP3 are proteins involved in the induction of thermogenesis in BAT and WAT respectively	Kajimura et al., 2015
	Leptin	Leptin regulates the levels of fat tissue is the body	Uchiyama et al., 2017

adverse (Manning et al., 2014).

The central melanocortin pathway consists of neurons that produce endogenous melanocortin ligands, derived from POMC [adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH) α-, β- or γ], five types of receptors for melanocortin (MCRs) and the endogenous melanocortin antagonist/inverse agonist AgRP (Shen et al., 2017). The melanocortin signaling is crucial to the appetite regulation and energy balance. The MC4R genetic deficiency cause severe young-onset obesity and theoretically MC4R agonists could induce weight loss at least in this specific group of patients. However, compounds targeting neural MCRs, especially MC4R with direct agonists, did not manage to proceed from clinical trial to the market due to significant cardiovascular incidences (Girardet and Butler, 2014). Recently novel approach to modulate MCRs has been described *via* indirect agonists acting through the AgRP-initiated signaling that provide opportunities to investigate new potential anti-obesity drugs with improved cardiovascular safety (Yang and Tao, 2016).

The NPY has a pivotal role in many physiological functions such as food intake, energy homeostasis, circadian rhythm, cognition and stress response. For example, by activating the Y1 and Y5 receptors in the hypothalamic AgRP/NPY neurons it stimulate the appetite (Reichmann and Holzer, 2016). Most of the designed NPY blockers revealed low selectivity, bioavailability, toxicity or tolerance that restrict their progress into clinical trials (Manning et al., 2014). It is suggested that targeting selectively peripheral Y-receptors might have the beneficial effect on energy homeostasis without affecting feeding behavior, mood and cognitive functions controlled within the brain (Yulyaningsih et al., 2011).

The endocannaboid system could be activated in a result of overeating, leading to decrease in energy expenditure and obesity development. The influence on appetite and metabolism of the eCBs are mediated through two types of cannabinoid receptors (CB) distributed both in the central nervous system in the periphery (Manning et al., 2014). The first selective CB1 receptor antagonist approved to treat obesity was rimonabant which was withdrawn shortly after its introduction to the European market, because independent reports suggested serious adverse events, including severe depression and suicidal thoughts (Cheung et al., 2013). Recent study examined the weight loss

potential of new generation CB1 antagonists designed to selectively bind the peripheral receptors, but not to penetrate the blood-brain barrier and thus to avoid the behavioral effects of the centrally active agents (Sharma et al., 2018).

The endogenous peptide neuromedin U (NmU) is provided from the lateral hypothalamus to the paraventricular nucleus (PVN) and was recently suggested as a novel regulator of food-driven behavior with anorectic action. Two types of NmU receptors are described to activate neurons of certain brain circuits. Activation of the NmU1 receptor stimulate the POMC neurons in ARC whereas the NmU2 receptors trigger neurosignalling in the PVN, both inhibiting hunger (Kaisho et al., 2017).

7.2. Transcription factors

Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily, consisting of three PPAR isotypes PPARα, PPARβ/δ and PPARγ, regulating genes implicated in inflammatory response and metabolic regulation. The PPARα is mainly expressed in the liver, where it regulates the fatty acid transport, β-oxidation and ketogenesis, PPARβ/δ is highly active in skeletal muscle and is involved in the response to exercise by improving lipid homeostasis and insulin sensitivity and PPARγ expression is highest in adipose tissues, where it modulates lipid uptake and adipogenesis by adipocytes (Gross et al., 2017). Currently available PPARγ agonists from the drug class of TZDs are used in the therapy of the non-insulin-dependent diabetes to increase the insulin sensitivity of the tissues. However, due to serious side effects of these drugs such as weight gain, cardiovascular events, hepatotoxicity and increased risk of liver failure there is need for novel class PPARγ ligands with better safety profiles (Wang et al., 2014b). Recent studies also suggest potential use of PPARα and PPARβ/δ ligands in obesity (Mueller, 2014).

Another family of transcription factors crucial for the adipocyte development which could provide potential targets in obesity management is the cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)/enhancer binding protein (C/EBP) superfamily consisting from several members C/EBPα, β, δ and C/EBP homologous protein (CHOP; Gupta, 2014). The CHOP is an endoplasmic reticulum stress-

inducible protein that regulates the cell metabolism, but its exact function has to be further investigated (Chikka et al., 2013). The C/EBPβ and C/EBPδ have been shown to participate in the early phases of adipogenesis whereas C/EBPα is expressed at later stages of differentiation and participates in a positive feedback loop with PPARγ to sustain adipocyte maturation (Mueller, 2014).

The sirtuins (SIRT), particularly SIRT1, have been extensively studied for their roles in calorie restriction-induced life span extension, as well as the prevention of aging-associated pathologies including metabolic dysfunctions (type 2 diabetes and obesity), cardiovascular disease, cancer, and neurodegeneration (Lee et al., 2014). The SIRT6, another member of the sirtuin family, localizes in the nucleus and primarily regulates chromatin signaling and genomic integrity. Its activation improves pathophysiological defects in various tissues that occur as a result of obesity and diabetes such as liver, adipose tissue, skeletal muscle and pancreatic β-cells. However, whether activators of the SIRTs could be beneficial for the treatment of such pathological conditions needs further investigations (Bae, 2017).

The nuclear erythroid-related factor 2 (Nrf2) is a transcriptional factor taking part in the cellular response against stress (Marchev et al., 2017b). At present, it is identified to counteract with chemical stressors, oversupply of nutrients, inflammatory mediators or accumulation of misfolded proteins within the cells (Hayes and Dinkova-Kostova, 2014). Recent data suggest that activation of Nrf2-KEAP1 pathway could plays a role in the pancreatic β-cell function, insulin sensitivity and thus may prevent the long-term complications of diabetes (Matzinger et al., 2017). Oxidative stress is one of the key factors involved in obesity-related health complications, and Nrf2 may be a promising drug target to treat them. However, studies using Nrf2 knock-out mice and KEAP1 knock-down mice, as well as, an Nrf2 agonist in obesity models show inconsistent results. Therefore, future studies are needed to elucidate the involvement of the Nrf2-KEAP1 pathway in obesity (Seo and Lee, 2013).

7.3. Enzymes

The AMP-activated protein kinase (AMPK) is an energy regulating enzyme acting in multiple tissues. Fasting activates the AMPK thus leading to increased fatty acid oxidation, glucose uptake and glycolysis, and inhibited fatty acid and glycogen synthesis. Considering its contribution to the control of energy metabolism at both the cell and whole-body levels, experimental studies suggest that exogenous activation of AMPK may induce weight loss in obese patients (Hardie, 2018).

The nicotinamide N-methyltransferase (NNMT) is a cytosolic enzyme recently described to play a role in the cellular energy homeostasis. The NNMT expression has been found to be up-regulated in the WAT of mice subjected to diet-induced obesity (DIO) model. Systemic treatment of the DIO mice with a selective NNMT inhibitor resulted in significant loss of body weight and WAT mass, reduction in adipocyte size, and corresponding improvements in the plasma lipid profile without affecting food intake nor produce any signs of toxicity or adverse behavioral effects which point out NNMT as viable target for potential anti-obesity agents (Neelakantan et al., 2018).

The protein-tyrosine phosphatase 1B (PTP1B) is an important negative regulator of the tyrosine phosphorylation cascade integral to the insulin and leptin signaling pathways (Cho, 2013). The PTP1B inhibitors are promising candidates for novel type of "insulin sensitizers" in the management of non-insulin-dependent diabetes, the MetS and obesity (Goldstein, 2001). Some small molecule inhibitors and PTP1B-directed antisense oligonucleotides investigated, which acts both centrally and peripherally, were reported to be in phase 2 clinical trials (Cho, 2013).

7.4. Protein targets

The suppressors of cytokine signaling (SOCS) are family of proteins that play an essential role in mediating inflammatory responses in both immune cells and metabolic organs such as the liver, fat and muscle tissues. The SOCS1 and SOCS3 play a role in controlling immune cells such as macrophages and T-cells, impact systemic inflammation, leptin and insulin resistance (Galic et al., 2014). The SOCS3 inhibitors could activate the signal transducer and activator of transcription 3 (STAT3) phosphorylation and eventually leads to improved sensitivity of the leptin signaling (Lubis et al., 2008).

Adiponectin is secreted from the fat cells as essential regulator of thermogenesis and mediate increased AMPK, PPARα ligand activities, fatty-acid oxidation, and glucose uptake. Deletion of adiponectin gene suppresses adrenergic activation, and down-regulates β3-adrenergic receptors, insulin signaling, and the AMPK-SIRT1 pathway in the BAT (Yamauchi et al., 2014). In obese individuals decreased adiponectin levels are found, thus potential strategies are discussed to reverse reduced adiponectin activity such as administration of adiponectin analogues or compounds that stimulate its expression (TZDs, soy protein, fish oils, and linoleic acid), activation of adiponectin receptors with selective agonists or activating antibodies (Liu and Sweeney, 2014).

Another regulator of the process of thermogenesis is the mitochondrial brown fat uncoupling protein 1 (UCP1), which produces heat by β-oxidation of lipids and glucose metabolism, instead of producing ATP (Kajimura et al., 2015). On the other hand the expression of UCP3 (an UCP1 analogue) could be induced by thyroid hormones, β3-adrenergic agonists and leptin, stimulating thermogenesis in muscles and BAT thus increasing the energy expenditure and the process of "browning" of the WAT. Targeting UCP1 and UCP3 as proteins inducing the thermogenesis is a novel strategy in the development of potential weight loss agents (Thyagarajan and Foster, 2017).

The discovery of leptin, in 1994, by Jeffrey Friedman laboratory initiated extensive experimental investigations over the last 20 years searching for novel anti-obesity agents targeting the leptin signaling (Morrison, 2009). However, up to date leptin replacement therapy is approved only in the treatment of certain types of lipodystrophy and very rare form of congenital obesity with leptin deficiency (Manning et al., 2014). The recent studies are focused on resolving the mechanisms and targeting the leptin resistance presented in obesity (Cui et al., 2017).

Despite this focus, newly approved anti-obesity drugs acting on these emerging targets are still missing which points out the need for elucidating more potent bioactive leads from synthetic, semi-synthetic or natural origin (Manning et al., 2014).

8. Traditional medicinal plants as powerful source of novel anti-obesity drugs

Plant-based medications that accelerate weight loss, proved to be safe, effective and widely available would be a preferable alternative for anti-obesity treatments (Martel et al., 2017). The biologically active food supplements for weight reduction are in the top 3 of the health products with highest sales, flooding the market with countless products that need to be regulated and standardized. Many of these claim to have natural origin and in the same time contain adulterants that are now known to be dangerous, for example, sibutramine (Skalicka-Woźniak et al., 2017). Thus, it is necessary to establish reliable parameters and correctly assess all the variables that mark a plant as a potent alternative in obesity therapy and warrant their safety (de Freitas Junior and de Almeida, 2017). In this context, the plants with anti-obesity effect could be classified in several categories according to their distinctive mechanisms, including (1) decreasing the lipid absorption, (2) decreasing the energy intake, (3) increasing the energy expenditure, (4) inhibiting the pre-adipocyte differentiation and proliferation, (5) decreasing lipogenesis and increasing lipolysis. As plant

extracts are multi-component systems they could also show their anti-obesity activities by a variety of mechanisms (Yun, 2010).

Current strategies for screening potent natural anti-obesity drugs involve the study of organic or water extracts of different parts (roots, leaves, fruits, flowers or seeds) of the medicinal plants, as well as, some related phytochemicals such as polyphenols, terpenoids, alkaloids, saponins, steroids and polysaccharides for their antihyperlipidemic, antihyperglycemic, carbohydrate and fat digestion reduction properties supported by their ability to modulate the molecular pathways and gene/protein expressions responsible of these activities (de Freitas Junior and de Almeida, 2017; Sompong et al., 2016; Spínola and Castilho, 2017). The suppression of the digestive enzymes, especially the pancreatic and gastric lipases, suppression of AMPK/malonyl Co-A signaling pathway or potential ghrelin antagonism that blunt the increased appetite or mediate the reduced expression of hypothalamic NPY or serum leptin (Yun, 2010), the increase of the energy expenditure *via* stimulating thermogenesis in muscles and BAT through the activation of UCP1 with natural compounds (Song et al., 2017b; Stohs and Badmaev, 2016) are the most widely studied mechanisms for determining natural products' beneficial effect in overweight and obese people (Sompong et al., 2016).

Since adipose tissue growth can be due to both hyperplasia and hypertrophy of adipocytes, the process of inhibiting proliferation and differentiation of pre-adipocytes and/or induction of apoptosis and stimulation of lipolysis in mature adipocytes are also possible opportunities to prevent and treat obesity. As an *in vitro* model to study this process 3T3-L1 murine pre-adipocytes cells are frequently used. Adipogenesis involves various stages and is regulated by several transcriptional factors, cell-cycle protein-regulated genes' expression, lipogenesis-related genes (Tung et al., 2017), adipogenesis-related enzymes, C/EBPs, PPARs, sterol regulatory element-binding proteins (SREBPs), fatty acid synthase (FAS) gene and acetyl-CoA carboxylase (ACC; Chaiittianan et al., 2017; Martel et al., 2017; Zhang et al., 2017).

The anti-obesity properties of plant extracts or isolated pure compounds could be evaluated by *in vitro* and *in vivo* studies. Selected examples of plant-derived molecules with well-established beneficial effects in obesity management are summarized in Fig. 4. The *in vitro* studies include two basic tests: inhibition on lipid accumulation in adipocytes and inhibition on pancreatic lipase activity, while the *in vivo* parameters comprise weight loss, lipid profile and food intake (Alonso-Castro et al., 2015).

8.1. In vitro studies

Hundreds of plant species have been screened for their activity to inhibit pancreatic lipase (Seyedan et al., 2015; Tung et al., 2017) and some other digestive enzymes (α-amylase, α- and β-glucosidase; Sompong et al., 2016) or to increase insulin sensitivity, supported with investigations of the molecular signaling pathways in several model cell lines, such as 3T3-L1, HEPG2 or L6 cells (Pan et al., 2017; Semaan et al., 2018). The present review summarizes some recent studies of plant extracts or pure isolated compounds with *in vitro* activity similar to that of the referenced drugs (*e.g.* Orlisat) used in obesity treatment. Selected examples are presented in Table 3.

Some of the most studied plants as natural pancreatic lipase inhibitors are different types of teas, such as oolong (Yuan et al., 2018), green (Nakayama et al., 2015; Seo et al., 2017) and black tea (Wang et al., 2017a,2017b). The identified polyphenols, *e.g.* gallocatechin (GC), epigallocatechin (EGC), epicatechin (EC), epigallocatechin gallate (EGCG), gallocatechin gallate (GCG) and epicatechin gallate (ECG) showed strong inhibitory activity against pancreatic lipase that is suggested to be due to the galloyl moieties within their chemical structures and/or polymerization of their flavan-3-ols (Jiang et al., 2017; Nakai et al., 2005). The non-esterified flavan-3-ols, such as (+)-catechin, (−)-epicatechin, (+)-gallocatechin, and (−)-epigallocatechin, showed zero and/or the lowest activities (IC$_{50}$ > 20 μM; Nakai et al., 2005).

Jiang et al. (2017) showed that although (−)-epigallocatechin 3-O-(3-O-methyl) gallate (EGCG3″Me) had better lipase and α-amylase inhibitory effect than the EGCG3″Me-phospholipids complex, the latter had facilitated transepithelial transport, suggesting the improved bioavailability and absorption of tea polyphenols and potential in development of functional foods (Jiang et al., 2017).

Ethanolic extracts of several Thai medicinal plant species such as *Memecylon edule* Roxb., *Garcinia vilersiana* Pierre, *Cryptoleptis elegans* Wall. and *Phyllanthus chamaepeuce* Ridl. produced the highest inhibitory activity of 90.97, 92.04, 94.64 and 95.38% at 100 μg/mL, respectively. The estimated activity was reported to be close to that of Orlisat (95.56%) and in positive correlation with the content of phenolic acids, flavonoids and alkaloids (Dechakhamphu and Wongchum, 2015). Aqueous extract of *Vitis vinifera* L., *Rhus coriaria* L., *Taraxacum syriacum* Boiss., *Rosmarinus officinalis* L., *Origanum dayui* Post also had pancreatic lipase inhibitory activity comparable with that of orlistat (IC$_{50}$ = 12.38 μg/mL). The observed activity was explained with the presence of some phenolic acids, such as caffeoylquinic, gallic, caffeic, protocatehuic, trans-caffeoyl tartaric and trans-coumaroyl tartaric acid, as well as, some flavonoids, *e.g.* myricetin-3-*O*-glucoside, quercetin-3-*O*-glucoside, quercetin-3-*O*-galactoside, quercetin, kaempferol-3-*O*-glucoside, kaempferol, myricetin, rhamnetin and isorhamnetin (Jaradat et al., 2017). The promising antihyperlipidemic and antihyperglycemic effects of *Syzygium aromaticum* L., *Phyllanthus amarus* Schumach. & Thonn., *Thunbergia laurifolia* Lindl at concentration of 1 mg/mL were confirmed by investigating the inhibition not only of the pancreatic lipase activity (21.42–85.93%), but also pancreatic cholesterol esterase (2.92–53.35%), intestinal maltase (5.16–44.33%), sucrase (1.25–45.86%), and pancreatic α-amylase activity (1.75–12.53%). In addition, inhibition of the cholesterol incorporation into micelles (6.64–33.74%), as well as, the bile acids binding (2.05–18.40%) was established (Sompong et al., 2016). Among 10 investigated Asteracea species *Argyranthemum pinnatifidum* Lowe var. *pinnatifidum*, *Helichrysum melaleucum* Rchb. Ex Holl, *Phagnalon loweli* DC revealed the most promising lipase inhibitory activity although lower than that of orlistat (IC$_{50}$ = 470 μg/mL), as well as, anti-diabetic potential due to the inhibition of α-amylase, α- and β-glucosidase. The observed activities were considered to be due to the presence of caffeoylquinic acids (Spínola and Castilho, 2017). Although the 80% methanolic extract from hot peppers (jalapeño) showed no lipase inhibitory activity, its main bioactive compounds quercetin, capsaicin, p-coumaric and caffeic acid were compared for their lipase inhibitory capacity with orlistat (Martinez-Gonzalez et al., 2017). Capsaicin revealed low pancreatic lipase inhibitory activity (Martinez-Gonzalez et al., 2017), but when used in high concentration (250 μM) decreased 90% of the lipase activity (Hsu and Yen, 2007).

Several terpenoids, such as corosolic, ursolic, 23-hydroxyursolic, asiatic and betulinic acids isolated from *Actinidia arguta* (Siebold & Zucc.) Planch. Ex Miq (Jang et al., 2008), carnosol, oleanolic and carnosic acid identified in *Salvia officinalis* L. (Ninomiya et al., 2004), as well as, several acetylated oleanane-type triterpene saponins (chakasaponin I, II and III) from *Camellia sinensis* (L.) O. Kuntze have been reported to exhibit significant lipase inhibitory activity (Yoshikawa et al., 2009). The alkaloid rich fraction from *Tabernaemontana divaricata* (L.) R. Br. Ex Roem. & Schult had higher lipase inhibitory activity (IC$_{50}$ = 7.86 μg/mL) than the total methanolic extract (IC$_{50}$ = 12.73 μg/mL), due to the main bis-indol alkaloid conophylline (IC$_{50}$ = 2.63 μg/mL). Other bis-indol alkaloids with lipase inhibitory activity from the same plant were conophyllinine, conophyllidine and taberhanine (Sridhar et al., 2017). The isoquinoline alkaloid stephalagine had more than 10 times higher lipase inhibitory activity that the ethanolic extract of *Annona crassiflora* Mart (Pereira et al., 2017).

Ethanolic extract of purple corn silk caused multiple-stages interruption on adipocyte life cycle at concentration between 25 and 1000 μg/mL and inhibited the pre-adipocyte proliferation between 43.52 and 75.51% in 3T3-L1 cells. More than 80% reduction of lipid

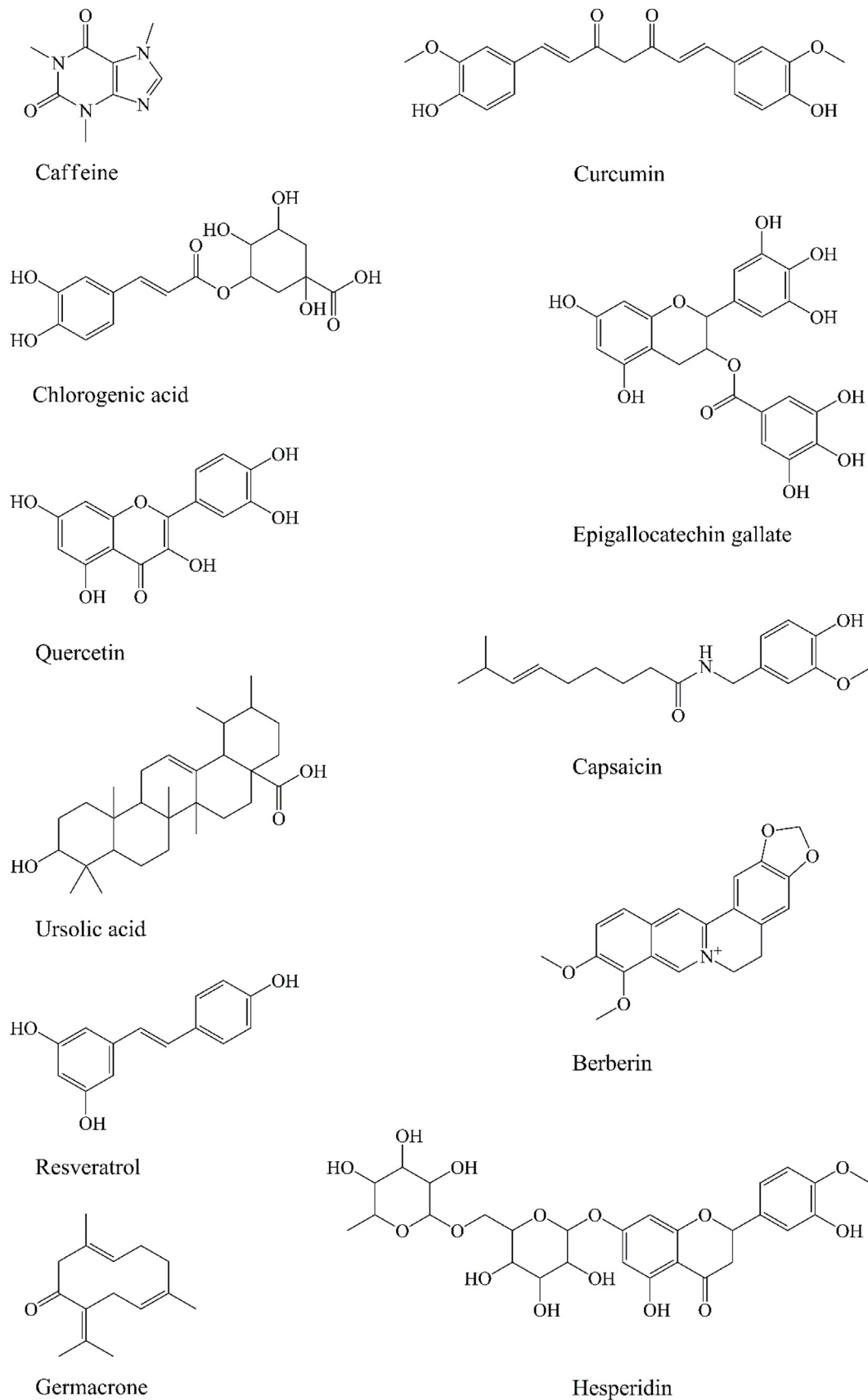Caffeine

Curcumin

Chlorogenic acid

Epigallocatechin gallate

Quercetin

Capsaicin

Ursolic acid

Berberin

Resveratrol

Germacrone

Hesperidin

Fig. 4. Chemical structures of common anti-obesity plant-derived compounds.

Table 3
In vitro lipase inhibitory activity of selected plant extracts and isolated pure molecules.

Plant species (incl. plant organ, extract type)	Inhibition (IC$_{50}$, µg/mL)	Reference
Annona crassiflora Mart (fruits, ethanolic)	104.50	Pereira et al., 2017
Argyranthemum pinnatifidum Lowe var. *pinnatifidum* (leaves, ethanolic)	3310	Spínola and Castilho, 2017
Brassica nigra L (leaves, aqueous)	91	Jaradat et al., 2017
Camellia sinensis (L.) O. Kuntze (flower buds, ethylacetate fraction of methanolic extract)	91	Yoshikawa et al., 2009
Cryptolepis elegans Wall (leaves, ethanolic)	0.30	Dechakhamphu and Wongchum, 2015
Fagonia arabica L (aerial part, 80% methanolic)	204.10	Bustanji et al., 2011
Garcinia vilersiana Pierre (leaves, ethanolic)	0.11	Dechakhamphu and Wongchum, 2015
Green tea (*Camellia sinensis* L) (leaves, aqueous)	76.20	Nakayama et al., 2015
Green tea (leaves, 50% methanolic)	480	Seo et al., 2017
Helichrysum melaleucum Rchb. Ex Holl (leaves, ethanolic)	3890	Spínola and Castilho, 2017
Hypericum triquetrifolium Boiss (aerial part, 80% methanolic)	107.70	Bustanji et al., 2011
Magnifera indica L (fruits, methanolic)	1.50	De Pradhan et al., 2017
Marva palviflora L (leaves, 50% ethanol and n-hexane)	23.70	Jaradat et al., 2017
Origanum dayui Post (leaves, 50% ethanol and n-hexane)	18.62	Jaradat et al., 2017
Phagnalon loweli DC (leaves, ethanolic)	3050	Spínola and Castilho, 2017
Phyllanthus chamaepeuce Ridl (leaves, ethanolic)	0.45	Dechakhamphu and Wongchum, 2015
Reseda alba L (aerial part, 80% methanolic)	738	Bustanji et al., 2011
Rosmarinus officinalis L (leaves, aqueous)	51.30	Jaradat et al., 2017
Rhus coriaria L (fruits, aqueous)	19.95	Jaradat et al., 2017
Salvia apinosa L (aerial part, 80% methanolic)	156.20	Bustanji et al., 2011
Salvia officinalis L. (leaves, methanolic)	94	Ninomiya et al., 2004
Taraxacum syriacum Boiss (leaves, aqueous)	39.80	Jaradat et al., 2017
Vitis vinifera L (leaves, aqueous)	14.13	Jaradat et al., 2017

Phytochemicals		
(−)-Epigallocatechin 3-O-(3-O-methyl) gallate	1140	Jiang et al., 2017
(−)-Epigallocatechin 3-O-gallate	0.16	Nakai et al., 2005
(−)-Epigallocatechin-3,5-digallate	0.06	Nakai et al., 2005
5-O-caffeoylquinic acids	310	Spínola and Castilho, 2017
1.5-O-dicaffeoylquinic acids	610	Spínola and Castilho, 2017
3.5-O-dicaffeoylquinic acids	500	Spínola and Castilho, 2017
p-Coumaric acid	27.92	Martinez-Gonzalez et al., 2017
Caffeic acid	72.33	Martinez-Gonzalez et al., 2017
Chlorogenic acid	59.80	Lunagariya et al., 2014
Gallic acid	80	De Pradhan et al., 2017
4-Hydroxybenzoic acid	160	De Pradhan et al., 2017
Hesperidin	32	Lunagariya et al., 2014
Isoorientin	31.60	Lunagariya et al., 2014
Quercetin	1.84	Martinez-Gonzalez et al., 2017
Kaempferol	33.02	Zhang et al., 2015
Oleanolic acid	83	Ninomiya et al., 2004
7-Methoxyrosmanol	32	Ninomiya et al., 2004
Royleanonic acid	35	Ninomiya et al., 2004
Carnosol	4.40	Ninomiya et al., 2004
Carnosic acid	12	Ninomiya et al., 2004
Ursolic acid	7.22	Jang et al., 2008
Betulinic acid	9.58	Jang et al., 2008
Corosolic acid	9.64	Jang et al., 2008
23-Hydroxyursolic acid	19.70	Jang et al., 2008
Chakasaponin I	206.95	Yoshikawa et al., 2009
Chakasaponin II	229.22	Yoshikawa et al., 2009
Chakasaponin III	653.68	Yoshikawa et al., 2009
Stephalagine	8.35	Pereira et al., 2017

accumulation at 500 µg/mL and moderate apoptotic inductive effect (40.35%) at 1000 µg/mL was observed. The authors explained the observed activity with the presence of phenolic acids, anthocyanins and flavonoids with quercetin derivatives being the dominant molecules (Chaiittianan et al., 2017). Standardized *Cirsium setidens* Nakai ethanolic extract (containing the marker compounds pectolinarin and pectolinarigenin) exhibited also antiadipogenic activity, suppressed the expression of lipogenic and increased the expression of lipolytic genes, *e.g.* at concentration of 200 µg/mL the lipid accumulation was decreased with 56% while the glycerol release was increased with 114.9%. The observed effects were mediated by inhibition of PPARγ, C/EBPβ and C/EBPδ, which are the early transcriptional factors indicating the initial adipocyte differentiation. The extract stimulated also the fatty acid oxidation in an AMK-dependent manner. The increased phosphorylation of AMK and ACC lowered the concentration of

malonyl-CoA, an endogenous inhibitor of carnitine palmitoyl transferase (CPT)-1 and the first enzyme in the β-oxidation of fatty acids (Cho et al., 2017a,2017b). These signaling pathways were studied during the treatment of 3T3-L1 cells with aqueous extract of *Baccharis trimera* (Less.) DC. At concentration of 1.0 mg/mL 90% reduction of these molecules was observed, considering that the extract has a potential to be used in development of functional foods (de Souza Marinho do Nascimento et al., 2017). Similar findings were reported by Gao et al. (2016) who studied the activity of EEG rich extract (astragalin, daphnoretin and tiliroside were identified) from *Edgeworthia gardneri* (wall.) Meisn. Treatment of 3T3-L1, L6 and HepG2 cellular models with methanolic extract of *Allophylus cominia* Sw. stimulated the glucose uptake through inhibition of PTP1B. The inhibition of this enzyme increased the insulin activity as well, *e.g.* the insulin EC$_{50}$ decreased from 1000 nM to 38 nM in the presence of the extract. Another observed

effect was the decreased lipid accumulation at the initial stage of the adipocytes differentiation, which could be related to the lypolitic activity of the extracts, triggered by an increase of intracellular cAMP levels (Semaan et al., 2018). Water extracts from *Arctium lappa* L. were also reported to have antiadipogenic effect mediated through inhibition of PPARγ, C/EBPα and activation the AMPK. On the other hand, inhibition of WAT differentiation and activation of BAT differentiation has been observed as well (Han et al., 2016). Seeds extract form *Cathamus tinctorius* L. down-regulate the adipogenic transcription factors SREBP1c and PPARγ and their target genes involved in the synthesis, transport, and storage of lipids at least partly *via* activation of AMPK pathway and thus inhibit the differentiation of the adipocytes (Hwang et al., 2016). A polyphenol rich extract (containing mainly glycosylated derivatives of cyaniding and malvidin, chlorogenic, p-coumaric, ferulic, caffeic and sinapic acids, as well as, quercetin, myricetin, kaempferol and laricitrin) from different berries inhibited adipogenesis through suppression of PPARγ, C/EBPα, SREBP1, adipocyte fattyacid-binding protein (aP2), FAS, lipoproteinlipase (LPL), hormone-sensitive lipase (HSL), perilipin 1 (PLIN1) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA expression in a dose-dependent manner (Kowalska et al., 2017). At IC_{50} dose of 22.5 μg/mL and 7.63 μg/mL extract from *Lysimachia foenum-graecum* and its active component foenumoside B inhibited the PPARγ induced preadipocyte differentiation and the expression of the lipogenic genes aP2, CD36 and FAS (Seo et al., 2011). A well-document molecule that inhibits also the adipogenesis in 3T3-L1 cells through the above mentioned mechanisms is capsaicin. Along with that capsaicin induced also apoptosis in these model cells through activation of caspase-3, Bax and Bak (proapoptotic proteins) and down-regulation of Bcl-2 (antiapoptotic protein). A loss in the mitochondria membrane potential and up-regulation of adiponectin was observed as well (Hsu and Yen, 2007). Some polyphenols such as isorhamnetin-3-O-D-glucuronide and ellagic acid isolated from *Sanguisorba officinalis* Linne also possess antiadipogenic properties (Im et al., 2017). Flavonoid glycosides (astragalin, isoquercetin, rhamnocitrin 3-O-glucoside, and nicotiflorin), triterpenes (methyl hederagenin) and triterpene glycosides (hederin, echinocystic acid 3-O-arabinoside and cauloside B) had a regulatory role in adipocytes differentiation. Some of them down-regulated lipid accumulation and insulin induced 3T3-L1 differentiation, reduced adipocyte size, while others decreased the levels of all adipogenic proteins and glucose transporter type 4 (GLUT4), but increased adiponectin (Nishina et al., 2017). Betulinic acid has been reported to have a strong lipolytic effect mediated by cAMP-dependent phosphodiesterase inhibition (Kim et al., 2012). Cucrumin has a certain beneficial effect on regulating glucose and lipid metabolism. At 20 μM concentration curcumin increased the glucose uptake in 3T3-L1 adipocytes 1.6 times and decreased the glycerol release 69% in comparison with the control. The observed effect was due to the increased mRNA expression for C/EBPα, PPARγ and PPARα (Pan et al., 2017).

Although the inhibition of pancreatic lipase, cholesterol esterase, α-amylase, α- and β-glucosidase are considered as markers for anti-obesity efficacy, the obtained results might not be relevant in a certain biological system. That is why further studies using animal models to verify the inhibitory activities *in vivo* are required (Alonso-Castro et al., 2015; Bustanji et al., 2011).

8.2. In vivo studies

The BW, body fat and the BMI are generally used to define obesity, while the lipid profile, including hepatic and blood levels of triglycerides (TG), total cholesterol (TC), LDL-cholesterol (LDL-C) and HDL-C are used to diagnose MetS. Increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are used as indicators for hepatic damage. For that reason these are of the most frequently investigated parameters in *in vivo* models of obesity (Ahn and Go, 2017). Summary of the main findings from recent *in vivo* studies are presented in Table 4.

Approximately 10% BW loss was reported by Ahn and Go (2017) after treatment of C57BL/6 mice (subjected to HFD for 12 weeks) with *Pinus densiflora* bark extract. The food intake, as well as, the food efficiency ratio [(weight gain/food intake) × 100] did not change significantly, which means that the extract did not induce a loss of appetite or an increase in food intake. The supplementations of this extract down-regulated *de novo* lipogenesis by reducing hepatic TG, TC, LDL-C and decreasing the fat distribution compared to the control group. The results were consistent with the lowered levels of the enzymes ACC1, FAS and stearoyl CoA desaturase 1 (SCD1). The reduction of adipogenesis was confirmed by inhibition of C/EBPα, PPARγ and perilipin. In the treated group the serum levels of ALT and AST were higher than in the control group, but still within the normal range (0–40 IU/L; Ahn and Go, 2017). Similar effects were achieved by administration of 50% ethanolic extract of *Sanguisorba officinalis* L. (Jung et al., 2016a). The standardized extract of *Cirsium setidens* reduced the BW, adipose tissue weight and improved the serum lipid profile through down-regulation of the adipogenesis markers and up-regulation of the enzymes boosting the fatty acid oxidation. The activation of AMPK responsible for shifting the lipid synthesis to fatty acid oxidation was observed (Cho et al., 2017a,2017b). At low doses (100 mg/kg/day) the methanolic extract of *Salvia officinalis* had better beneficial effect on glucose tolerance, insulin sensitivity, lipid profile, body weight gain and food intake compared to the high dose of 400 mg/kg/day. This might be due to the presence of palmitic acid in the extract, which leads to insulin resistance in higher concentrations. The extract also increased significantly the plasma levels of the anti-inflammatory cytokines (IL-2, IL-4 and IL-10) and decreased the pro-inflammatory IL-12, TNF-α and keratinocyte-derived chemoattractant/humangrowth-regulated oncogene (KC/GRO). The improved insulin sensitivity was explained by the presence of PPARα and PPARγ agonists α-linoleic, γ-linoleic, carnosic, oleanolic, ursolic acid and carnosol (Zaibi et al., 2018). *Agrimonia pilosa* Ledeb aqueous extract ameliorated insulin resistance in HFD rats by decreasing the inflammatory response (TNF-α and IL-6) and increasing the adiponectin (Jang et al., 2017). The polyphenol-rich extract of *Vitis vinifera* L. grape skin prevented the obesity induced by HFD through increasing the insulin sensitivity in adipose tissue and skeletal muscle due to increase in AMPK and GLUT4 expression. The observed hypoglycemic and antioxidant effects contributed to the regulation of the lipid profile and adipokines, by favoring the reduction of the inflammation in adipose tissue and weight gain (da Costa et al., 2017). The sesquiterpene germacrone (20 mg/kg/day) was the active molecule of *Garcinia cambogia* extract, which at concentration of 200 mg/kg/day attenuated hyperlipidemia by alleviating fatty acid synthesis/uptake and improve lipid metabolism by stimulation of FA β-oxidation (Guo and Choung, 2017). Another molecule – arctiin – isolated form *A. lapa* was considered to be responsible for the weight loss in HFD-induced obese mice by reducing the mass of the WAT and inhibition of adipogenesis, through activation of liver kinase B1 (LKB1), which is constitutively active and phosphorylates AMPK (Han et al., 2016). Some triterpene saponins, such as foenumoside B, isolated from *L. foenum-graecum* inhibited adipocyte differentiation through expression of genes involved in lipid metabolism towards lipid breakdown. Moreover, the inhibition of some pro-inflammatory cytokines in adipose tissue suggested its protective role against insulin resistance (Seo et al., 2012). Extract of *Morinda citrifolia* L. leaves (60% ethanolic) improved the metabolic disruptions caused by obesity regarding the tricarboxylic acid cycle, glucose, choline, and creatinine and gut microbiota metabolism in Srague-Dawley rats. After treatment for 9 weeks with 50 mg extract/kg/day, 7.9% reduction of the BW was observed (Jambocus et al., 2017). An improvement in Bacteriodetes/Firmicutes ratio in the gut of DIO mice through enrichment of the Proteobacteria population and reduction of the Deferribacters population was achieved by administration of *Polygala tenuifolia* extract (Wang et al., 2017a,2017b).

A novel target mechanism for obesity management is the modulation of KEAP1-NRF2 and PKC/NF-κB signaling pathways. The

Table 4
Examples of selected plant extracts studied as potential anti-obesity agents *in vivo* in rodent models.

Plant species (incl. plant organ and extract)	Dosage, mg/kg/day	Period of treatment, weeks	Weight loss, % (from initial BW)	Main findings	Reference
Agrimonia pilosa Ledeb (aerial parts, aqueous)	100	16	3.80	Ameliorated insulin resistance; decreased TNF-α, IL-6 and increased adiponectin in serum	Jang et al., 2017
Arctium lapa L (fruits, 70% ethanolic)	100	10	11.50	Decreased weight gain and adipose tissue mass; reduction of TG and LDL-C; suppression of C/EBPα and PPARγ; activation of AMPK and UCP1	Han et al., 2016
Cinnamomum cassia Presl (cortex, aqueous)	100	16	15.25	Decreased serum levels of glucose and insulin; decreased hepatic TG, TC, LDL-C and ALT; suppressed lipid accumulation; decreased adipocyte size and increased muscle mass	Song et al., 2017a,2017b
Cirsium setidens Nakai (leaves, ethanolic)	100	8	10.50	Decreased serum levels of TG, TC and LDL-C; decreased adipocytes differentiation; down-regulation of C/EBPα, PPARγ, FABP4, SREBP-1 and FAS; up-regulation of adiponectin and CPT-1	Cho et al., 2017a,2017b
Garcinia cambogia L (commercial extract)	200	4	10.50	Attenuation in plasma glucose, serum insulin, leptin and hepatic lipid levels; attenuation of hyperlipidemia (down-regulation of FAS, SREBP-1, SREBP-2); inhibition of ACC1 and PPARγ; stimulation of FA β-oxidation	Guo and Choung, 2017
Hippophae rhamnoides L (seeds, petroleum ether)	300	9	43.51	Decreased levels of TG, TC and LDL-C; up-regulation of PPARα in liver; down-regulation of PPARγ in liver and adipose tissue; down-regulation of TNF-α in adipose tissue	Yang et al., 2017
Lysimachia foenum-graecum Hance (whole plant, ethanolic)	300	8	7.94	Reduced insulin resistance; reduced inflammatory cytokines (IL-6 and IL-1β) and reduced levels of PPARγ and C/EBPα in fat tissue	Seo et al., 2011
Melissa officinalis L (leaves, aqueous ethanol)	800	4	44.00	Decreased adipose tissue mass; reduced mRNA levels of adipose tissue angiogenic factors	Woo et al., 2016
Pinus densiflora Siebold & Zucc (commercial extract)	50	12	10.80	Decreased levels of TG, TC and LDL-C; decreased levels of ACC1, SCD1, SREBP-1; inhibition of C/EBPα, PPARγ and perilipin	Ahn and Go, 2017
Platango albicans L (leaves, dichloromethane)	300	7	13.68	Decreased TG, TC and LDL-C in serum; increased antioxidant enzymes SOD, CAT and GSH-Px	Samout et al., 2016
Polygala tenuifolia Willd (roots, aqueous)	250	5	7.00	Improved gut microbiota; inhibited lipid accumulation; attenuation of low-grade chronic inflammation	Wang et al., 2017a
Salvia officinalis L (leaves, 80% methanolic)	100	5	12.60	Improved insulin sensitivity (decreased blood glucose and plasma insulin levels); increased anti-inflammatory cytokines (IL-2, IL-4, IL-10) and reduced pro-inflammatory cytokines (IL-12, TNF-α, KC/GRO); decreased levels of TG, TC and LDL-C	Zaibi et al., 2018
Sanguisorba officinalis L (leaves, 50% ethanolic)	200	8	21.32	Decreased levels of (TG, TC and LDL-C); down-regulated C/EBPα, PPARγ, FABP4 and ACC; up-regulated adiponectin and CPT-1	Jung et al., 2016b
Vitis vinifera L (seeds, hydroalcoholic)	200	12	25.00	Improved insulin sensitivity (modulation of insulin signaling proteins); modulation pAMPK/AMPK ratio and GLUT4 expression in muscle and adipose tissue; restoration of antioxidant activity (SOD, CAT and GSH-Px); reduced anti-inflammatory markers (TNF-α and IL-6); decreased levels of TG, TC and LDL-C	da Costa et al., 2017

administration of polyphenol-rich extract from *Molineria latifolia* rhizomes neutralized the systemic oxidative stress-related parameters without affecting the renal and liver functions in the diabetic rats. Analyses on adipose, muscle and liver tissues demonstrated differing ability to scavenge free radicals and protection against lipid peroxidation (Ooi et al., 2018). Another polyphenol-rich extract from *Plantago albicans* reduced the BW, lipid accumulation in liver and heart tissue of DIO rats and improved the lipid profile, activating a panel of antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) (Samout et al., 2016).

8.3. Clinical studies

Due to the prevalent and often uncontrolled use of plant extracts in obesity management, evidence from human studies is required to support claims of efficacy and safety. The main outcome measures evaluated in clinical trials are antropometric parameters such as BW, BMI, WC, HC, WHR, FFM, FM. Additional tests are done usually to evaluate the effect on appetite, overall physical health (blood pressure, heart rate), changes in lipid profiles (TG, TC, HDL-C, LDL-C), glucose, insulin, leptin and ghrelin levels (Hasani-Ranjbar et al., 2009).

In a systematic review Hasani-Ranjbar et al. (2009) summarized clinical trials investigating various combinations of plant extracts or plant-derived compounds and most of these studies showed anti-obesity effects such as decreasing BW in humans with or without changes in body fat. Ephedrine, caffeine and EGCG are among the most frequently included natural compound in such combinations (Hasani-Ranjbar et al., 2009; Kapoor et al., 2017). Another recent review assessed the commonly available natural supplements used to inhibit the appetite for obesity control and management in humans using a systematic search of clinical trials meeting an acceptable standard of evidence (Astell et al., 2013).

In this present review as examples for human studies of plant extracts with anti-obesity activities 12 randomized clinical trials (RCTs) were included, 10 reporting supplementation with certain extract and 2 with herbal combinations. The RCTs reported random allocation of humans to herbal products *vs* placebo with or without specific dietary and exercise programs outlined in Table 5. The main inclusion criteria were defined to be the BMI varies between 25 and 40 kg/m^2, WC > 80 cm for women and WC > 94 cm for men. None of the included RCTs reported serious adverse events from the supplementation with the tested herbal preparations (Cho et al., 2017a,b; Dostal et al., 2016a, 2016b; Gilardini et al., 2016; Loftus et al., 2015; Samavat et al., 2016).

The largest and with longest duration clinical trials evaluated cohort of women supplemented with *Camelia sinensis* L. decaffeinaited catechin-rich extract. However, the evidences that the green tea extracts are effective in reducing body weight in these recently published RCTs were mostly inconclusive (Dostal et al., 2016a, 2016b; Samavat et al., 2016). Within the studied herbal preparations in the selected RTCs *Aster spathulifolius* extract (Cho et al., 2016) and a combination containing *Imperata cylindrica* Beauvois, *Citrus unshiu* Markovich, and *Evodia officinalis* Dode (Cho et al., 2017b) were the only exceptions that achieved weight reduction greater that 3% from initial weight within 12 weeks, but with very small number of participants included.

In spite of the reviewed data from clinical trials there is scanty of information regarding the toxicity of the plant extracts or phytochemical preparations. Systematic investigations in this aspect are missing and only few case reports have been mentioned, e.g. *Larrea tridentata* (DC.) Coville exhibited acute hepatotoxicity effect by inhibition of cyclooxygenase and cytochrome P-450; *Thevetia peruviana* (Pers.) K. Schum. induced cardiotoxicity, gastrointestinal and neurological disorders; administration of *Rhamnus purshiana* DC has been associated with hepatotoxicity and hypokalemia (Alonso-Castro et al., 2015).

Another safety issue is that in many countries the plant-derived anti-obesity products are labeled as food supplements and do not pass through strict licensing regulations, which may lead to distinguishable

abuse with the products' authenticity, exposing to a risk the human health (Alonso-Castro et al., 2015). Different platforms for determining the quality and authenticity of the raw plant material and final herbal product have been constantly developing. They include broad range of classical to modern analytical techniques, *e.g.* nuclear magnetic resonance (NMR) spectroscopy, high performance liquid chromatography (HPLC), ultra HPLC (UHPLC), gas chromatography and liquid chromatography-mass spectrometry (GC-MS and LC-MS) and in some case combined with DNA-barcoding supervisory method (Skalicka-Woźniak et al., 2017). The NMR-based metabolomics is an useful tool in terms of quality control, since it allows obtaining structural information for a wide range of compounds in complex plant extracts or commercial products with a high analytical precision (Georgiev et al., 2015). This technique has been successfully applied in development of procedures for detection of marker phytochemicals found in a definite plant or commercial product, thus confirming their authenticity (Booker et al., 2016; Marchev et al., 2017a).

The relative lack of compelling evidence to suggest the efficacy and safety of weight loss herbal supplements confirms the findings of previous literature reviews and highlights the need for more prolonged RCTs with greater number of participants and more detailed authentication of the plant extracts used (Astell et al., 2013; Hasani-Ranjbar et al., 2009; Skalicka-Woźniak et al., 2017).

9. Conclusions

Obesity is a multifactorial disease that has reached epidemic extent and is becoming a public health burden of the highest order, hence the term globesity was introduced. It has a complex etiology comprising several risk factors, including lack of energy balance, genetic, neuroendocrine, behavior, social and environmental factors, as well as, intake of drugs that cause overweigh or obesity as a side effect. However, the chronic low-grade inflammation as a consequence of obesity compromises the healthy secretion profile of pro and anti-inflammatory adipokines and increases the risk of developing insulin resistance, heart and vascular diseases, respiratory and metabolic disorders and cancers. Various strategies including lifestyle changes, bariatric surgery and pharmacotherapy have been applied to reduce obesity and inflammation. Despite the advances in the field of obesity ethiology and pathology there is still lack of effective therapeutic options. At the present moment there are only few anti-obesity drugs approved for long-term use with orlistat being the most common. Further studies are needed to clarify the role of the newly identified targets, such as receptors for neuropeptides, transcription factors, enzymes and proteins and how their modulation could benefit obese individuals. The active exploration of many natural sources, including medicinal plants may lead to developments based on a growing understanding of the complex and highly redundant physiological mechanisms involved in body fat content regulation. Ethnopharmacological approaches have increased over the years, becoming an important scientific tool in selection of plant species for *in vitro* and *in vivo* studies that test the efficacy, safety and quality of anti-obesity pharmacological activity. Further investigations should be focused on the elucidation of the bioactive compounds, to clarify the molecular mechanism and to verify the main effective phytochemicals. Still the main focus is the effects of phytochemicals on WAT, especially the process of adipogenesis and lipogenesis and alleviating the excessive energy on expanding adipose tissue. More solid scientific evidences from pre-clinical and clinical studies are necessary to evaluate the anti-obesity impacts of bioactive food compounds individually or in combination.

All the plant extracts or bioactive molecules summarized in this review are likely to be promising sources of anti-obesity compounds for development of novel science-based natural product formulations. In spite of the great number of the herbal supplements that claim to have weight loss effect, only few have been tested to prove their efficacy in

Table 5
Examples of herbal extracts studied as potential anti-obesity agents in double blind, placebo controlled randomized clinical trials.

Plant species (incl. plant organ and extract)	Dosage, mg/day	Period of treatment, weeks	Weight loss,% (from initial BW)	Main findings	Reference
Aster spathulifolius Maxim (leaves, 50% ethanolic)	700	12	4.30	BW reduction within the treated group as well as between the groups (placebo vs extract: − 0.08 ± 2.11 kg vs −3.30 ± 3.15 kg); BFM (−2.38 ± 2.30 kg), BF% (−1.87 ± 2.12%) and WC were decreased within the extract group	Cho et al., 2016
Camellia sinensis L. (leaves, decaffeinaited catechin-rich extract)	1500	12	1.40	Decrease in WC and levels of TC and LDL-C; no significant differences in BW and BMI or WC when compared to placebo group	Chen et al., 2016
Camellia sinensis L. (leaves, decaffeinaited catechin-rich extract)	1315	52	0.26	No statistically significant differences from baseline to week 52 in BW, BMI or any body-compositionvariable between or within treatment groups	Dostal et al., 2016a
Camellia sinensis L. (leaves, decaffeinaited catechin-rich extract)	1315	52	0.23	No statistically significant differences in changefrom baseline to week 52 in BW, BMI or WC between or within treatment groups	Dostal et al., 2016b
Camellia sinensis L. (leaves, decaffeinaited catechin-rich extract)	1315	52	NA	No statistically significant differences in changefrom baseline to week 52 in BW, BMI or TC and LDL-C between or within treatment groups	Samavat et al., 2016
Coleus forskohlii (Willd.) Briq. (roots, ethanolic standardized for 10% forskolin)	500	12	1.60	No statistically significant differences in changefrom baseline to week 12 in BW, BMI or WC between or within treatment groups. However, the extract administration significantly improved insulin and IR	Loftus et al., 2015
Gynostemma pentaphyllum (Thunb.) Makino (leaves, 50% ethanolic)	3000	12	1.70	Reduced BW, BMI and BF within extract treated group, but no significant differences when compared to placebo group	Park et al., 2014
Hibiscus sabradiffa L. (flos, aqueous)	450	12	1.30	Reduced BW, BMI and BF within extract treated group, but no significant differences in when compared to placebo group	Chang et al., 2014a
Punica granatum L. (fruits, commercial extract)	1000	4	2.50	Significant decrease in serum insulin and HOMA-IR in the extract group vs placebo with association to the mean BW reduction in the extract group	Hosseini et al., 2016
Zingiber officinale Roscoe (rhizomes, 60% ethanolic)	2000	12	1.20	No significant differences from baseline to week 12 in BW, BMI or WC between or within treatment groups	Ebrahimzadeh Attari et al., 2015
Commercial herbal combinations					
Greenselect Phytosome® combination of Camellia sinensis, soy distearoylphosphatidylcholine and pure piperine from Piper nigrum L.	450	12	NA	The proportion of obese women who maintained aweight loss > 5% was greater in the supplemented than in the placebo	Gilardini et al., 2016
Imperata cylindrica Beauvois, Citrus unshiu Markovich, and Evodia officinalis Dode (commercial extracts)	2400	12	3.60	Statistically significant difference in BW reduction within the treated group as well as between the groups (placebovsextract: −1 kg vs −2.7 kg); BFM (−1.6 kg), BF% (−1.5%) and WC were also significantly decreased	Cho et al., 2017a,2017b

NA- No data available for the body weight at the end of the treatment period.

humans. The main reason for that is the poor reproducibility if the clinical trials, as well as, underestimation of the toxicity assessment, which should be taken in consideration. Tight licensing regulations, including establishment of safety standards based on strict quality control through all manufacturing stages are essential for development of plant-derived products for obesity treatment with certified quality.

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Transparency document

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