Interventions to reduce metabolic sequelae in rodent models of diet-induced obesity

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ABSTRACT — Obesity is one of the top ten adverse health conditions in the world and it has doubled in the last decades. Altered maternal nutrition, including both undernutrition and maternal obesity, have been shown to lead to transgenerational transmission of metabolic disorders in the offspring, perpetuating metabolic disorders in the future generations. Several interventions have been performed in animal models of obesity to reduce the long-term obesity-related sequelae and consequently the adverse effects on offspring's health. Our aim was to critically review studies that performed interventions with natural/botanical compounds in rodent model high fat diet (HFD) induced obesity and to assess glucose, lipid, metabolic and cardiovascular outcomes. We carried out a computerized literature review using PubMed and Medline. We identified fourteen studies that fulfilled the inclusion criteria. Lipid profile, in term of adipogenesis, leptin, triglycerides, cholesterol and adiponectin levels, improved after administration of all the natural compounds tested. Glucose profile improved with the supplementation of rice hull smoke extract, rheum undulatum, zanthoxylum piperitum DC ethanol extract and alpinia officinarum showing an increased insulin sensitivity. Oxidative stress and body weight also improved after the supplementation with most of the compounds in rodent models of obesity, proving promising and effective anti-obesity properties. These experimental studies demonstrate that several natural interventions improve lipid, glucose and oxidative profiles in rodents presenting an obese phenotype induced by a high fat diet consumption. Clinical research could now explore the efficacy and safety of such interventions in the obese population to reduce the long-term sequelae of this metabolic disfunction and thus to interrupt the vicious circle that an obese mother generates a child prone to develop metabolic (and cardiovascular) disease in adult life.

KEYWORDS
Natural compounds, Rodent Model, Obesity, High Fat Diet

INTRODUCTION

The World Health Organization (WHO) declared obesity as one of the top ten adverse health risk conditions in the world and one of the top five in developed nations [1]. Recent WHO data estimate that the worldwide prevalence of obesity has doubled between 1980 and 2014. In 2014 more than 1.9 billion adults, 39% of the population, aged 18 years and over (38% of men and 40% of women) were overwei-

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gh; of these over 600 million, 13% (11% of men and 15% of women) were obese[1]. Traditionally obesity has been linked to changes in diet and lifestyle, as result of increased high caloric dietary intakes, of high-energy diets and concomitant reduced physical activity levels[2]. Human and animal studies have highlighted the link between the perturbations of the intrauterine environment, occurring in the early-life, and the increased susceptibility to obesity and related metabolic and cardiovascular disorders later in life. Altered maternal nutrition, including both undernutrition and maternal obesity, has been shown to lead to transgenerational transmission of metabolic disorders in the offspring, perpetuating then, in the future generations (Figure 1). This association has been conceptualized by Barker and others as the "Developmental origins of health and diseases" also known as "The Barker's hypothesis"[3] which states that, environmental factors impacting the fetus during critical developmental periods can cause adverse lifelong effects on offspring's health. More recent studies had demonstrated that fetal developmental programming is a transgenerational phenomenon that transmits the programming effects to subsequent generations, even in the absence of continuous environmental stressors, thus perpetuating a cycle of obesity and metabolic disorders in future generations[4]. The role of the interactions between environmental and genetic factors in the contribution to complex polygenic obesity and common obesity is really important as no efficient treatment, apart from major surgery, currently exists[5]. Therefore, by the discovery of novel genes or new etiological pathways, innovative therapies, preventive measures, and pharmacogenetic strategies can be found and/or used in obesity studies.

FETAL PROGRAMMING

A quarter of a century ago, Barker and Osmond[6] at the University of Southampton, England, crystallized the concept of fetal programming and early origin of adult disease by suggesting that stress in utero, manifested by low birth weight (LBW), increased the risk of cardiovascular disease and stroke in specific areas of England and Wales. Prior researchers had formulated similar hypotheses on the basis of findings in humans[7,8] and animals[9]. Hales and Barker[10], however, provided a mechanistic explanation by proposing the "thrifty phenotype hypothesis" to complement the already existing "thrifty genotype hypothesis"[11]. According to Hales and Barker's hypothesis, fetuses exposed to suboptimal conditions during intrauterine life, reprogram physiological developmental processes in anticipation of similar suboptimal conditions in postnatal life. If postnatal conditions are instead optimal and resources

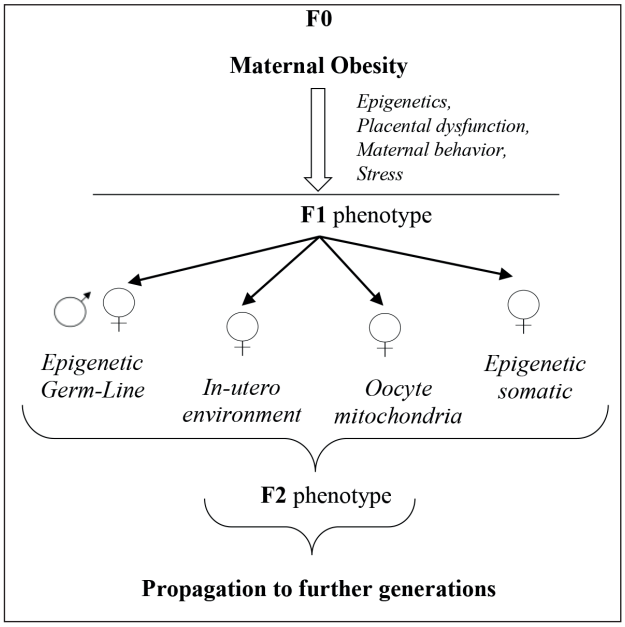

Figure 1. Mechanisms by which developmental programing in the F0 generation can be transmitted to the F3 generation and beyond via either the maternal or paternal lineage. Adapted from Nestlé, Ann Nutr Metab 2014.

are abundant, the organism is ill-prepared to cope with the different environment and hence is more susceptible to develop diseases[12].

EPIGENETIC MECHANISMS

Epigenetics is a term coined by Waddington (1969)[13] to describe heritable gene function changes without a changed DNA base sequence. Epigenetics has become a central mechanism in the hypothesis of fetal developmental programming. There are several different epigenetic mechanisms as: activation or inactivation of genes by DNA methylation (DNA methylation suppresses gene expression), histone acetylation and chromatin remodeling regulatory feedback by microRNAs. Obesity and its related comorbidities are intimately associated with epigenetic alterations. The implicated genes, also called epi-obesogenic genes, are susceptible to epigenetic regulation and they play a role in the development of obesity by controlling processes such as adipogenesis, inflammation, appetite and glucose tolerance[14]. New genome loci that could be part of the epigenetic map of obesity have been discovered after an analysis of 450 million cytosine with a guanine as the next nucleotide (CpG) sites[15]. Dick et al[16] have associated increased BMI and adiposity with raised DNA methylation at hypoxia-inducible transcription factor 3A (HIF3A) – a gene that could affect gene expression management involved in obesity development. Therefore, knowing the combination of both genetic and epigenetic information in obese patients would improve personalized interventions[17].

Nutritional imprinting on hormonal and epigenetic mechanisms

The hypothalamic pituitary adrenal axis and the insulin-like growth facto axis may have a crucial role in the regulation induced by nutritional programming. The persistent alterations seem to be a consequence, at least in part, of elevated insulin levels during 'critical periods" of pre-natal and early postnatal development. Also, leptin seems to play an important role in this complex system. New knowledge about these mechanisms involved suggests the development of new, rational and effective preventive and/or therapeutic options before and/or after birth. Thus, early infancy may provide an opportunity for intervention aimed at reducing later disease risk[18].

Animal models of obesity

Several animal studies have been created to examine the effects of maternal metabolic disorders during pregnancy on offspring's development later in life. These studies have been conducted in different animal species: sheep, non-human primates and mostly rodents. Along the years, different models of metabolic disorders have been developed in mice and rats, including pharmacologically induced diabetes, using streptozocin, as well as transgenic model with mutation in the leptin pathway as: the ob/ob mouse[19], the dB/dB mouse (the "diabetic" mouse)[20]. In both, humans and rodents, the development and/or maintenance of obesity has been assumed to result from diet-induced leptin resistance[21-23]. In fact, after exogenous administration of leptin, obese individuals do not respond with a decrease food intake that is normally observed in lean individuals and are, hence, considered leptin-resistant[24,25]. These leptin-resistant models are obtained by inducing a deficit in the down-streaming process of the brain leptin receptor: proopiomelanocortin (POMC) knockout mouse, POMC/AgRP (Agouti related protein) knockout mice, and many others. The model that we decided to focus on in this review is the diet-induced obesity model. It is a polygenic model of rats and mice that include a diet-induced obesity (DIO) and diet resistant (DR), which means that they gain weight and fat at the same rate as chow-fed controls[26]. The high fat diet (HFD) is the most used because it rapidly and specifically reduces the central actions of insulin and leptin. This effect is rapid, occurring after a few days of HFD exposure and it seems to directly affect the respective intracellular signaling pathways in hypothalamic target neurons with resulting changes in neuropeptide expression (e.g. lack of an insulin effect on POMC expression), but possibly also in other brain areas. Fat composition seems to have a major role in this effect because saturated fat (e.g. palmitic acid) is more deleterious than unsaturated fat[27].

Natural/botanical drugs as an alternative effective anti-obesity therapeutic strategy

Several interventions have been performed in animal models of obesity to ameliorate weight gain, blood pressure, glucose and insulin regulation, leptin levels, lipid metabolism and vascular functions. It is of remarkable importance that anti-obesity drugs, such as orlistat and sibutramine, have serious side effects including valvular heart disease[28]. Under the guidelines of the US Food and Drug Administration, botanical drugs can be developed faster and more cheaply than conventional single-entity pharmaceuticals. Thus, there are many botanical products that might provide safe, natural and cost-effective alternatives to synthetic drugs[29,30]. Recent studies have found that natural bioactive compounds, including resveratrol, curcumin, green tea and brown rice can be used to treat obesity in obese mouse and rat model[31-34]. Thus, in this review we will analyze the studies that tested the administration of natural compounds in diet-induced rodent model of obesity.

METHODS

The research question of this review was defined as: what are the interventions with natural compounds performed in rodent models of obesity induced by high fat diet? Eligibility criteria were pre-determined by reviewers to prevent bias in the inclusion or exclusion of articles and to improve the precision of the broader search.

Inclusion Criteria:

- Obesogenic diet: high fat/high fructose diet (Fat content > 30% of total energy content) from weaning for 4 consecutive weeks. The obesogenic diet was defined as any diet in which fat and fructose, regardless of type or source, constituted greater than 30% of the total energy (kJ) content.
- Studies involving rodents model: rats and mice.
- Studies testing the effects of the administration of natural/botanical compounds.
- Controlled studies in which the control groups included rodents fed with standard chow/control diet or rodents that didn't receive the treatment.

Exclusion criteria:

- All not rodents' studies.
- All not rodents' studies. All not controlled studies.
- All not rodents' studies. Studies testing the efficacy of drugs or synthetic compounds.
- All not rodents' studies. Experimental studies conducted during pregnancy.
- Studies were excluded if they did not meet the above definition, or if the macronutrient content of the diet was not specified or ambiguous.

Using PubMed and Medline we found 14 studies that met the inclusion criteria, which had been conducted in obese mice and/or rats models, precisely, rats and mice genetically modified to develop insulin resistance or hypertension and not genetically modified susceptible to diet-induced obesity.

Interventions with natural compounds performed in rodent models of high fat diet-induced obesity

The interventions that had been performed in the 14 studies conducted in rodents are the following:

1. Selenium-enriched probiotics (SP): is essential in the human diet. It is a new product developed using different strains of probiotics that can transform and enrich organic selenium (Se) form inorganic source, which has a strong ability to convert sodium selenite into organic Se. Studies of dietary SP supplementation showed that this combination has a positive effect in lowering body weight, lipid levels, antioxidative status, and gene expression[35].
2. Black Garlic: Garlic (Allium sativum) has been used as a medicinal ingredient in folk remedies since the old times. It contains various bio-functional properties affecting health[36,37]. Black garlic is made by ripening raw garlic at high temperature and humidity, which removes the peculiar pungent odor[38], it gets its name from the black hue of the cloves but retains the same shape as raw garlic. During the ripening process, the glyco-component and amino acids of the garlic undergo a non-enzymatic browning reaction, producing melanoidins and water-soluble components such as S-allylcysteine (SAC) and S-allyl melcaptocystein (SAMC) and nearly removing all volatile substances[39], these substances play a key role in antilipidemic action as well as conferring potent antioxidant activity[40].
3. Soy leaf (SL): known to be useful for the prevention and/or treatment of obesity because of its composition with kaempferol glucosides or pterocarpans. Coumestrol, the most abundant pterocarpan found in soy leaves, is a potent antioxidant of low-density lipoprotein and inhibits yeast a-glucosidase[41]. Soy isoflavonoides possess antioxidant, anti-inflammatory, and anti-cancer effects[42,43].
4. Resveratrol: Isolated from the oriental medicinal plant Polygonum capsidatum exerts a variety of pharmacological effects, such as anticancer and anti-inflammation actions[44]. Resveratrol exerts a strong inhibitory effect on production of reactive oxygen species and it has free radical scavenging properties. It was shown to prevent adult hypertension, vascular dysfunction and microvascular rarefaction in male offspring following fetal exposure to a low-protein diet[45].
5. Rice hull smoke extract (RHSE): it has been shown to reduce the cellular lipid content in 3T3-L1, preadipocyte cells, by about 72% and 88%. RHSE has a strong antiadipogenic effect exerted by suppressing the expression of the adipocyte differentiation adiponectin marker[46].
6. Eriobotrya Japonica (EJ) and Nelumbo Nucifera (NN): are fruit plants widely used in India, China, Japan, and Korea for their medicinal values. EJ and NN are rich in several flavonoids (luteolin, quercetin, rutin, isoquercetin, tannins, and triterpenoids) and alkaloids. Several researchers have reported their anti-inflammatory, antioxidative, anticancer, antidiabetic, anti-obesity, and many other biological activities[47].
7. Cydonia oblonga mill leaf extract (COM Rosacea): also called Kinashi, Soil papaya, Biye, is a traditional Uyghur medicinal plant, commonly used in Western China, for the treatment or prevention of cardiovascular disease, among other. In traditional Uyghur medicine COM fruit, leaves, roots, branches and other parts are used as medicine for the treatment or prevention of cardiovascular disease. Currently, there is much research being done on the chemical composition and antibacterial effects of COM and on its effects on coagulation and blood pressure[48].
8. Blueberry peel extract (BB): are polyphenols that have shown promising results treating cognitive impairment, ischemic heart disease, oxidative stress, and neurological degeneration[49]. Ethanol extracts from the BB leaf, stem, root, and fruits contained active compounds with insulin-like and glitazone-like properties and protected against glucose toxicity[50]. In obese people, the consumption of BB improved metabolism at dietary achievable doses[51].
9. Fucoxanthin (Fxn): is one of the most abundant carotenoids and contributes more than 10% of the estimated total production of carotenoids in nature, especially in the marine environment[52]. It was found that fucoxanthin significantly reduced plasma and hepatic triglyceride concentrations and cholesterol-regulating enzyme activities, and fecal triglyceride and cholesterol[53] as well as fatty acid oxidation enzyme activity in epididymal white adipose tissue of mice[54,55]. The potential lipid lowering effect might be mediated by down-regulating various lipogenic enzyme activities and upregulating fatty acid β-oxidation activity suggesting that fucoxanthin might act as a regulator of lipid metabolism in fat tissues[56].
10. Rheum undulatum L. (RU): is a perennial herb that is distributed and cultivated mainly in South Korea[57]. The rhizome of the species is one of the important herbal medicines that are used wi-

dely as anti-inflammatories and anti-blood stagnation agents in East Asia[58,59]. Recently, it was found that RU and 3 compounds isolated from it (desoxyrhapontigenin, emodine, and chrysophanol) showed significant anti-obesity and antidiabetic activity based on the oral glucose tolerance test[58].

11. Green Tea Polyphenols: is one of the most popular beverages in the world. The impacts of green tea consumption on weight loss have been reported in clinical[60-62] and laboratory animal studies[63]. Such an anti-obesity effect of green tea is probably due to its capacity in elevating thermogenesis and fat oxidation, lowering lipid peroxidation[64,65], as well as suppressing appetite and nutrient absorption[66].
12. Zanthoxylum Piperitum DC ethanol extract (ZPDC): has been used in Korea as a traditional medicine for vomiting, diarrhea, and abdominal pain. The fruit and leaves of ZPDC contain aliphatic acid amides, terpenoids, flavonoids, an alkaloid, and other phenolic which exhibit antioxidant and hepatoprotective effects. Previous studies[67] reported that a glycoprotein isolated from ZPDC possesses anti-inflammatory properties.
13. Germinated brown rice GBR: has been seen as one of the most interesting germinated cereal products and it has garnered a great deal of attention, especially in Asian countries[68]. During the process of germination, the chemical compositions of the rice change drastically because the biochemical activity produces essential compounds and energy for the formation of the seedling. Germination is therefore considered an important way to improve bioactive compounds and health benefits of rice grains[69].
14. Alpinia Officinarum (AO): has been used in traditional medicine for the treatment of abdominal pain, emesis, diarrhea, impaired renal function and dysentery. Recently, it has been found to have also anti-obesity properties [70].

Diet-induced obese rodent model

Female and male C57BL/6J, C57BL/6N and Albino mice were placed on different varieties of high-fat diet (HFD) specified in Table I, to develop an obese phenotype. Female and male Sprague-Dawley (SD) rat were placed on high-fat diet after weaning to obtain an obese phenotype (Table I).

MAIN FINDINGS

The results of the 14 studies included in this review were evaluated focusing mostly on glucose and lipid metabolisms and oxidative and biophysical status (oxidative stress, body weight or weight gain) (Table II). Each one of the interventions showed a certain degree of improvement in the obesity parameters evaluated.

LIPID PROFILE

In the rodent obesity models considered, we found that the lipid profile and metabolism were improved by all the natural compounds. Precisely, lipid accumulation in white adipose tissue, liver and lipid cellular content were decreased by Black Garlic, Resveratrol, Rice hull smoke extract (RHSE), Eriobotrya japonica and Nelumbo nucifera, Zanthoxylum piperitum DC ethanol extract, Germinated brown rice and Alpinia officinarum. RHSE inhibited the AMPK signaling pathway and might serve as an anti-obesity multifunctional food additive considering that AMPK, a major regulator for cellular energy homeostasis, has an important role in the development of obesity, because AMPK up-regulates lipid and glucose homeostasis by controlling the expression of PPAR and SREBP1c during adipogenesis (Choi et al.,2013).

Cell survival rate in pre- and mature adipocytes as well as the proliferation rate of preadipocytes were decreased by Resveratrol, Blueberry peel extract and Alpinia officinarum. All the other compounds showed an improvement in terms of plasmatic leptin, adiponectin, cholesterol, and triglycerides levels.

GLUCOSE PROFILE

Glucose homeostasis was improved by the administration of Black Garlic, Rice hull smoke extract, Rheum undulatum, Zanthoxylum piperitum DC ethanol extract, Eriobotrya japonica plus Nelumbo nucifera and Alpinia officinarum. All of them demonstrated decreases in blood glucose and insulin levels, increasing the insulin sensitivity.

HEPATIC STATUS

Positive changes of serum AST and ALT levels, which are serum markers of liver damage, have been reported after treatment with Selenium-Enriched Probiotics, Black Garlic, Eriobotrya japonica plus Nelumbo nucifera and Cydonia oblonga mill Leaf extract. Moreover, Cydonia oblonga mill Leaf extract reduced liver steatosis, Fucoxanthin and Zanthoxylum piperitum DC ethanol extract lowered mRNA expression of hepatic Acetyl-CoA carboxylase (ACC) and fatty acid synthetases (FAS), while Germinated brown rice and Alpinia officinarum significantly decreased lipid accumulation in the liver.

Table I. Interventions with natural/botanical compounds in rodent models of diet-induced obesity.

Reference	Intervention	Duration and quantity of treatment	Animal Model
Agostinho Nido et al[71]	Selenium-Enriched Probiotics	Selenium content: 0.05 mg/kg for mouse	Female Albino mice at 4 weeks on HFD: high-fat diet was composed of 15% lard, 1 % cholesterol, 0.3% cholic acid, and 83.7% basal diet
Ha et al[72]	Black Garlic	High-fat diet + 0.5% or 1.5% black garlic extract for 5 weeks	4 weeks old male Sprague-Dawley rats on HFD
Li et al[73]	Soy Leaf	HFD + SLE: 50 mg kg^{-1} / day^{-1} for 8 weeks and for 16 weeks	8 weeks old male C57BL/6J mice on HFD: 45% kcal fat diet
Chang et al[74]	Resveratrol	Dosages ranging from 1 to 30 mg/kg treatment for 10 weeks	10 weeks old male C57BL/6C mice on HFD: 45.3% of calories from fat
Kim et al[75]	Rice hull smoke extract	Dietary supplementations of 0.5% and 1% RHSE for 7 weeks	4 weeks old male C57BL/6N mice on HFD
Sharma et al[76]	Eriobotrya japonica and Nelumbo nucifera	The mixture of NN and EJ leaves extracts was blended to 1:1 ratio. Sample resuspended in medium and filtered by a 0.22 μM filter for use in cell culture	6 weeks old male C57BL/6J mice on HFD: 60% fat
Abliz et al[48]	Cydonia oblonga mill. Leaf extract	Cydonia oblonga Mill. Leaf extract at low (80mg/kg/d), medium (160mg/kg/d), and high dose (320mg/kg/d) for 56 days	Sprague Dawley rats equally male and female, on HFD: 73.2% of feed, with1.5% cholesterol, 15% lard, 0.3% cholate, 10% egg yolk powder
Song et al[77]	Blueberry peel extract	HFD+BPE: 60 mg/kg administered for 5 weeks	5 weeks old male Sprague- Dawley (SD) rats on HFD: 60% kcal fat
Ha et al[56]	Fucoxanthin	High fat diet with 0.2% fucoxanthin for 4 weeks	4 weeks old male Sprague-Dawley rats on HDF: 20% fat (13% lard and 7% soybean oil)
Lee et al[78]	Rheum undulatum	RU 100 mg/kg for 8 weeks	Mice on HFD
Lu et al[79]	Green Tea Polyphenols	Concentration GTP 0.5%, wt/vol in the drinking water for 20 weeks	Virgin Sprague Dawley female rats on HFD: 45% of fat
Gwon et al[67]	Zanthoxylum piperitum DC ethanol extract	0.5% ZPE supplemented to the HFD	4 weeks old male C57BL/6J mice on HFD: 20% fat (lard 50, coconut butter 70, cocoa oil 30, corn oil 50 g/kg) and 0.5%
Ho et al[69]	Germinated brown rice	0.15% GBR methanol extract-administrated for 7 weekS	4 weeks old male C57BL/6J mice on HFD: 175g/kg of lard and 2,5 g/kg of cholesterol*
Jung et al[70]	Alpinia officinarum	Alphinia officinarum ethanol extract was 22.1% for 8 weeks	Male C57BL/6J mice on HFD: The experimental diet contained 20% fat and 0.5% cholesterol

*Ingredient HFD: Casein 200, Corn starch 284, Sucrose 50, Dextrose 132, Cellulose 50, Soybean oil 50, Lard 175, Cholesterol 2.5, Mineral mixture 35, Vitamin mixture 10, TBHQ 0.014, Sodium cholate 5, L-Cystine 3, Choline bitartrate 2.5 (g/kg).

BODY WEIGHT

Significant reductions in the body weight were obtained after the supplementations with most of the natural compounds tested, among those we find: Black Garlic, Soy Leaf, Rice hull smoke extract, Eriobotrya japonica and Nelumbo nucifera, Blueberry peel extract, Green Tea Polyphenols. Zanthoxylum piperitum DC ethanol extract, Germinated brown rice and Alpinia officinarum.

OXIDATIVE STRESS

One of the other most widely recognized characteristics of obesity is the increased oxidative stress[80]. Anti-oxidant properties have been shown by Selenium-Enriched Probiotics, Soy Leaf, Cydonia oblonga mill Leaf extract, Blueberry peel extract, Fucoxanthin, Green Tea Polyphenols, stemming from their ability to scavenge reactive oxygen species.

Table II. Effects of natural compounds interventions performed in murine models of HF-diet induced obesity.

Interventions	Animal Models	Outcomes	References
Selenium-Enriched Probiotics	Albino Mouse	↓ WG ↑ lipid metabolism, ↑antioxidative status, ↓ histopathological lesions, ↓ liver damages, reversed AST, ALT, TC, TG, LDL, TP, HDL, ↓ PPARα	Agostinho Nido et al[71]
Black Garlic	Rats	↓ Body weight, ↓total lipids and TG, ↓ plasmatic glucose and insulin levels ↓SREBP-1, ↓ ACC, FAS, ↓ G6PDH, ↓hepatic expression of HMG-CoA reductase and ACAT	Ha et al[72]
Soy Leaf	Mouse	↑ HSL, ↑CPT-1, ↑UCP2	Li et al73
Resveratrol	Mouse	↓ WG, ↓ lipid in adipose tissues and liver, ↓PPARγ, inhibited TNFα and adipogenic differentiation in preadipocytes and suppressed lipolysis in mature adipocytes	Chang et al[74]
Rice hull smoke extract	Mouse	↓ cellular lipid content, ↑AMPK, ↓ PPARγ, ↓C/EBPα, ↓ WG, ↓ epididymal white adipose tissue, ↓ TC, ↓TG levels in ↓ leptin ↓adiponectin levels, ↓ GOT/GPT enzymes,↓ blood urea, ↓ serum creatinine	Kim et al[75]
Eriobotrya japonica and Nelumbo nucifera	Mouse	↓WG, ↓ lipid accumulation, ↓PPARγ, ↓ hepatic TG, ↓TC, ↓ plasma glucose, ↓plasma insulin, ↓ALT, ↓AST	Sharma et al[76]
Cydonia ob. mill. Leaf extract	Rat	↓TC, TG, LDL-C and MDA, inhibited the activity of ALT, AST and LPS, ↑HDL-C content, ↑activity of SOD, GSH-PX, LPL and HL, ↓liver steatosis	Abliz et al[48]
Blueberry peel extract	Rat	↓ WG, ↓ C/EBPb, ↓C/EBPa and ↓PPARc genes, ↓ adipogenic activity	Song et al[77]
Fucoxanthin	Rat	↑HDL, ↓TC, ↓TG. Lower mRNA expression of hepatic ACC, FAS, G6PDH. ↓Hepatic mRNA expression of HMG-CoA and ACAT, ↑LCAT	Ha et al[56]
Rheum undulatum	Mouse	↓Body weight, ↓liver weight mediated by ↑PPARα and CPT1 in the liver, ↑adiponectin, aP2, and UCP3 in adipose tissue, ↓total and LDL-cholesterol levels, ↓ PTP1B activity and ↑insulin sensitivity	Lee et al[78]
Green Tea Polyphenols	Rat	↓Body weight, restored the expression levels of the following genes: 3 orexigenic genes (Agrp, Ghrl, and Nr3c1); 7 anorectic genes (Apoa4, Cntf, Ghr, IL-1b, Ins1, Lepr, and Sort); and 2 genes that relate to energy expenditure (Adcyap1r1 and Adrb1)	Lu et al[79]
Zanthoxylum piperitum DC ethanol extract	Mouse	↓ WG gain, ↓white adipose tissue mass, ↓serum TG, ↓cholesterol levels, ↓ lipid accumulation, ↓PPARγ, ↓C/EBPα, ↓SREBP-1, and FAS protein and mRNA levels in the liver	Gwon et al[67]
Germinated brown rice	Mouse	↓WG, ↓lipid accumulation in the liver and epididymal adipose tissue, ↓TG, ↓TC. ↓CCAAT, ↓SREBP-1, ↓PPAR	Ho et al[69]
Alpinia officinarum	Mouse	↓ Lipid accumulation 3T3-L1 preadipocytes, ↓C/EBPα, ↓SREBP-1, ↓PPAR-γ. ↓body, liver, and white adipose tissue weights, ↓decreased serum insulin, ↓leptin	Jung et al[70]

WG: Weight Gain; GSH-PX: glutathione peroxidase; HSL: Hormone-sensitive lipase; GPT: glutamate pyruvate transaminase; ACC: Acetyl-CoA carboxylase; HMG-CoA: Hydroxy-3-methylglutaryl coenzyme A; TC: total cholesterol; SOD: Superoxide Dismutase; CPT-1: carnitine palmitoyl transferase; SOD: superoxide dismutase; LPL: Lipoprotein lipase; ACAT: Acyl-CoA cholesterol acyltransferase; TG: triglycerides; PPARα: peroxisome proliferator-activated receptor-α; UCP2: Mitochondrial uncoupling protein 2; C/EBPα: CCAAT-enhancer binding protein; SREBP-1: Sterol regulatory element-binding protein 1; PTP1B: protein-tyrosine phosphatase 1B; TP: total protein; G6PDH: Glucose-6-phosphate dehydrogenaseAMPK: AMP-activated protein kinase; FAS: Fatty acid synthetases; GOT: glutamate oxaloacetate transaminase; LCAT: lecithin-cholesterol acyltransferase

Table III. Summary of the effects of the supplementation with natural compounds in rodent models of HFD-induced obesity.

	Rodent Model of HFD-induced Obesity			
	Glucose Profile	Lipid Profile	Body Weight	Oxidative stress
Selenium-Enriched Probiotics	NA	↑	/	↓
Black Garlic	↑	↑	↓	NA
Soy Leaf	NA	↑	↓	↓
Resveratrol	NA	↑	NA	NA
Rice hull smoke extract	↑	↑	↓	NA
Eriobotrya japonica and Nelumbo nucifera	↑	↑	↓	NA
Cydonia ob. mill. Leaf extract	NA	↑	/	↓
Blueberry peel extract	NA	↑	↓	↓
Fucoxanthin	NA	↑	NA	↓
Rheum undulatum	↑	↑	NA	NA
Green Tea Polyphenols	NA	↑	↓	↓
Zanthoxylum piperitum DC ethanol extract	↑	↑	↓	NA
Germinated brown rice	NA	↑	↓	NA
Alpinia officinarum	↑	↑	↓	NA

↑ = Improved; ↓ = Reduced; / = No changes; NA = Not Assessed.

DISCUSSION

According to this review, as it is summarized in Table III, the interventions with natural/botanical compounds analyzed are able to ameliorate different components of the obese phenotype induced by HFD, such as the lipid and glucose metabolisms, the oxidative status and body weight in animal models of HFD-induced obesity. Overall, the studies analyzed showed indeed significant decreases in TG, TC and insulin levels, but also in excessive lipid accumulation in the liver. The natural compounds analyzed, significantly decreased histopathological lesions, liver damages, reversed AST, ALT, TC, TG, LDL, TP, PPARα, PPARγ decreased lipid in adipose tissues and liver, which are the key sign of a fatty liver disease, regulating hepatic lipogenesis, they increased levels of lipoprotein lipase (LPL), hormone-sensitive lipase (HSL), HDL content and intensified activity of superoxide dismutase. They also brought to a decrease in body weight, leptin and adiponectin levels, inhibited TNFα and adipogenic differentiation in preadipocytes and suppressed lipolysis in mature adipocytes, less cellular lipid content and epididymal white adipose tissue, decreased serum insulin. The anti-obesity effects of the above-mentioned natural substances followed the activation of different pathways and mechanisms and all of them led to positive changes in several features of the obese phenotype. Our findings raise the possibility or profit of natural compounds and herbal formulation for the prevention and treatment of obesity or its related diseases. Other potential interventions remain to be investigated to permit evidence-based changes in the clinical management of obese patients. Ideally, according to the beneficial effects shown, a combination of natural compounds and approaches may lead to even better results for the treatment of obesity, to finally interrupt the vicious circle that an obese mother and/or father generate a child prone to develop metabolic and cardiovascular disease in adult life[81].

Conflicts of interest:
The Authors declare that there are no conflicts of interest.

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