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Review

Obesity Rodent Models Applied to Research with Food Products and Natural Compounds

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Abstract: Obesity is a disease whose incidence has increased over the last few decades. Despite being a multifactorial disease, obesity results essentially from excessive intake of high-calorie foods associated with low physical activity. The demand for a pharmacological therapy using natural compounds as an alternative to synthetic drugs has increased. Natural compounds may have few adverse effects and high economic impact, as most of them can be extracted from underexploited plant species and food by-products. To test the potential anti-obesogenic effects of new natural substances, the use of preclinical animal models of obesity has been an important tool, among which rat and mouse models are the most used. Some animal models are monogenic, such as the *db/db* mice, *ob/ob* mice, Zucker fatty rat and Otsuka Long-Evans Tokushima fatty rat. There are also available chemical models using the neurotoxin monosodium glutamate that induces lesions in the ventromedial hypothalamus nucleus, resulting in the development of obesity. However, the most widely used are the obesity models induced by high-fat diets. The aim of this review was to compile detail studies on the anti-obesity effects of natural compounds or their derivatives on rodent models of obesity as well as a critical analysis of the data.

Keywords: fatness; overweight; animal model; diet-induced obesity; high-fat diet; bioactive compounds

Citation: Martins, T.; Ferreira, T.; Nascimento-Gonçalves, E.; Castro-Ribeiro, C.; Lemos, S.; Rosa, E.; Antunes, L.M.; Oliveira, P.A. Obesity Rodent Models Applied to Research with Food Products and Natural Compounds. *Obesities* **2022**, 2, 171–204. https://doi.org/10.3390/obesities2020015

Academic Editor: Nobuyuki Takahashi

Received: 8 February 2022
Accepted: 2 April 2022
Published: 6 April 2022

1. Introduction

Obesity is defined as the excessive accumulation of fat in adipose tissue, resulting from an imbalance in consumption patterns, energy expenditure, and physical activity [1]. Despite the number of studies and available information to prevent or treat obesity, it has been considered a worldwide emerging health problem which continues to increase. The World Health Organization (WHO) estimates that there are more than 1.9 billion overweight adults, of which at least a third are obese [2]. The causes of this disease are complex and multifactorial. However, there is a genetic predisposition for obesity. Factors such as lifestyle, cultural and environmental influences, and epigenetics play a fundamental role in the development of obesity (Figure 1) [3–5]. People with excessive weight also tend to have a higher risk of developing other non-communicable diseases, such as type 2 diabetes, hypertension, osteoarthritis, cardiovascular, neurodegenerative, gastrointestinal, and chronic respiratory diseases, and certain types of cancer, contributing to a higher risk of premature death [6].

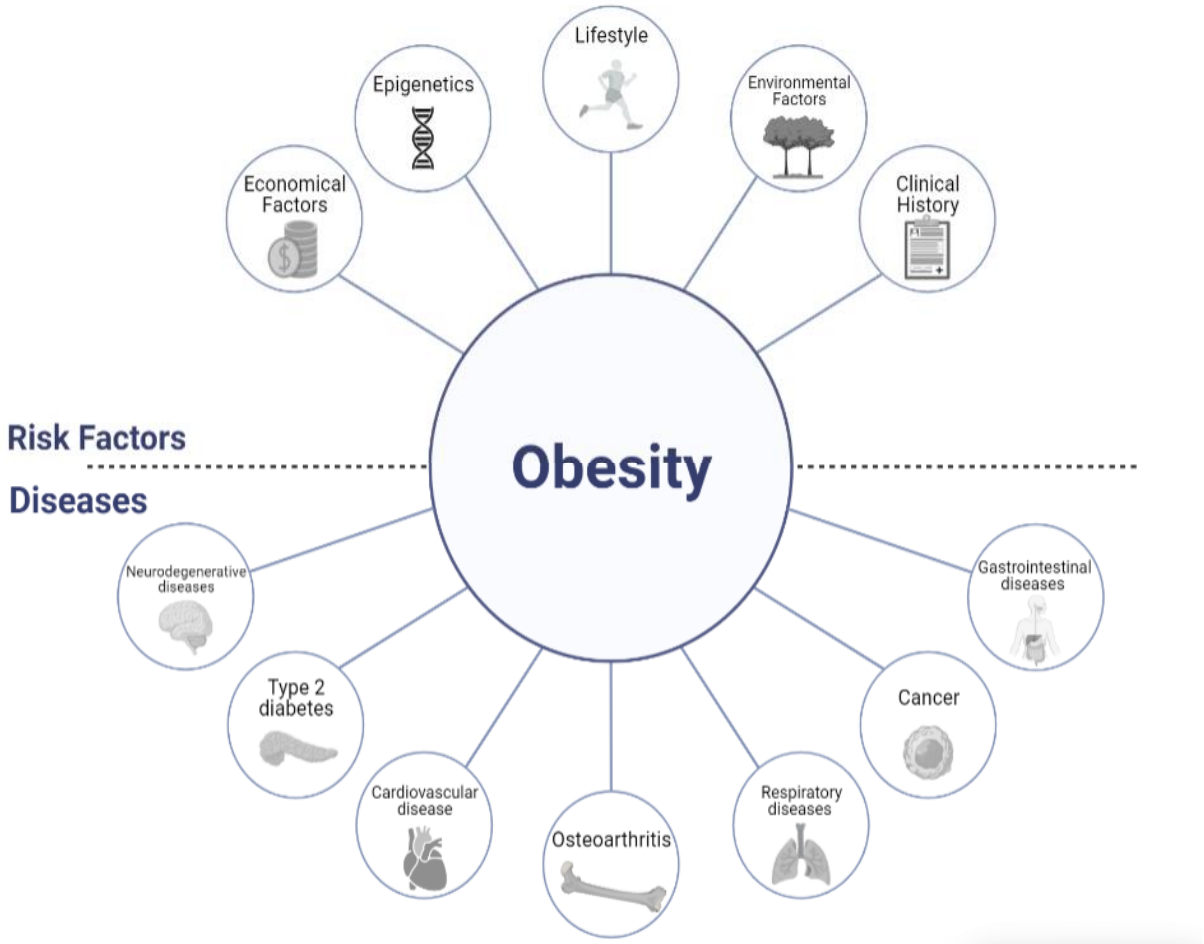

Figure 1. Risk factors and diseases associated to obesity.

Nowadays, two possible types of obesity treatments are available: physiological and pharmacological. The first, involves diet and behavior changes, but fails more frequently if it is not strictly followed by the patients. Currently, pharmacological therapy includes the following synthetic drugs: phentermine, diethylpropion, fluoxetine, sibutramine, orlistat and rimonabant [7]. Plants have been used by humans since primitive times for food and medicine. Due to the presumably adverse effects of synthetic food additives on human health and the increased consumer perception of this problem, there is currently a growing interest in natural compounds extracted from human diets [8,9]. Nutraceuticals and functional foods have become popular in human diets since their effects on preventing nutrition-related diseases and improving physical and mental well-being have been reported [10,11]. Crude extracts or isolated pure natural compounds have the potential to reduce body weight and prevent diet-induced obesity [7]. The use of animal models of obesity with dietary intervention is useful to understand the role of certain nutrients and the anti-obesity mechanisms of natural compounds [12]. In this review, we will focus on different animal models of obesity used to evaluate the effects of natural products or their derivatives and summarize the main anti-obesity outcomes.

2. Rodent Models of Obesity Used in Natural Compounds Research

Similar to other areas of biomedical research, rodents (rats and especially mice) are widely used as preclinical animal models to study the underlying mechanisms of obesity and to evaluate new therapeutic approaches [13–16]. The anatomical and physiological similarities between humans and rodents allow for the screening of potential natural compounds with therapeutic properties before applying new compounds on humans [11,17].

There are several animal models of obesity, but not all are used to study the effects of natural compounds. Some of the available models are monogenic (animals with single-gene disorders) such as the *db/db* mice, *ob/ob* mice, Zucker fatty rat and Otsuka Long-Evans Tokushima fatty rat, others are chemically induced models using the neurotoxin monosodium glutamate (MSG) which induces lesions in the ventromedial hypothalamus (VMH) nucleus, and the most widely used are the obesity models induced by diets (Figure 2).

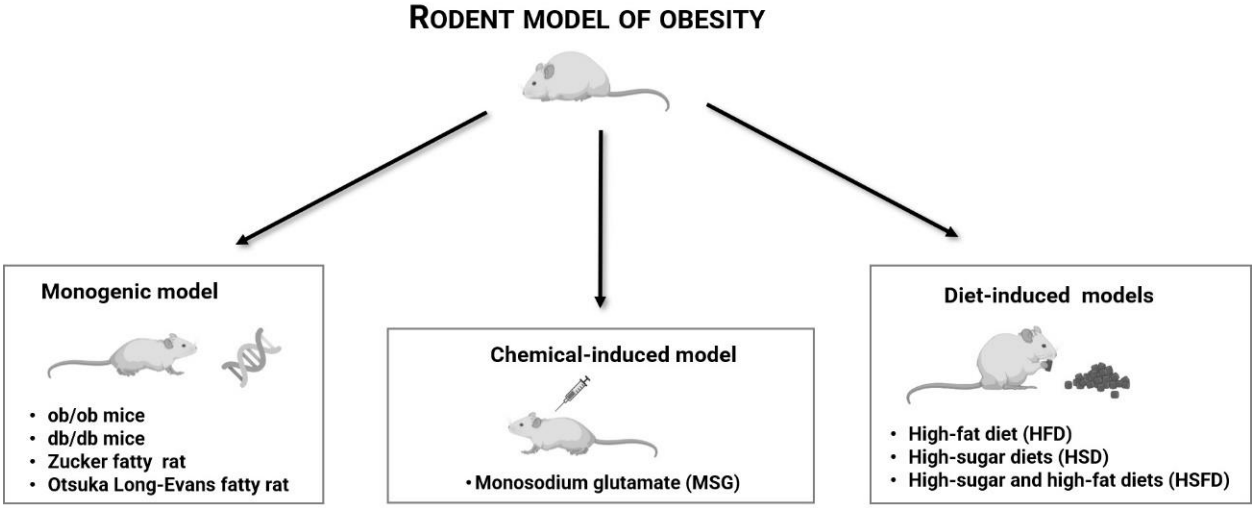

Figure 2. Rodent models of obesity that can be applied to natural compounds research.

2.1. db/db Mice

The *db/db* mouse (*db* stands for diabetes) [18] can be used to study the molecular basis of obesity; however, it is commonly used for studies concerning type 2 diabetes [19]. These *db/db* mice were developed by investigators from the Jackson Laboratories in 1966 and are phenotypically similar to the *ob/ob* mouse model. They exhibit a mutation in leptin receptor gene, in an autosomal recessive trait that encodes for a G-to-T point mutation, leading to defective leptin signaling [19,20]. The predominant mouse strain in which this mutation is maintained is the C57BL/KS [14,19]. The *db/db* mice are characterized by hyperphagia, a consequence of impaired leptin signing in the hypothalamus, develop early-onset obesity due to low energy expenditure, are insulin resistant, have decreased insulin levels and are hypothermic. Moreover, they develop dyslipidemia, hypogonadism, hyperglycemia, have growth hormone (GH) deficiency, and are infertile [18,20]. Regarding the analysis of natural products on obesity development, this model can become an option, especially when the compounds that are tested, such as *Artemisia* extract (artemether) and barley (Table 1), have supposedly a double effect on both obesity and diabetes [21,22].

2.2. ob/ob Mice

Developed at Jackson Laboratories in 1966, the *ob/ob* mice are homozygous for the obese spontaneous mutation in the leptin gene that prevents the secretion of bioactive leptin resulting in leptin deficiency [1,14,18]. Leptin is a hormone derived from adipocytes, and its deficiency leads to an increase in appetite and the development of severe obesity [23–25]. The homozygous mutant mice are typically of the C57BL/6J strain. These mice present a pronounced obese phenotype characterized by uncontrollable food intake, type 2 diabetes, hyperphagia, hyperleptinemia, insulin resistance and fatty liver, hepatic steatosis, hypogonadism, and hypothyroidism [19,20]. The *ob/ob* mice are a better model for studying obesity than *db/db* mice because they have a longer lifetime and fewer clinical signs [26]. The effects of natural compounds such as celastrol, genistein, cannabinoid Δ9-tetrahydrocannabivarin and cinnamon extract on the *ob/ob* mouse model can be analyzed in Table 1 [27–30].

2.3. Zucker Fatty Rat

The Zucker fatty rat (ZFR), or Zucker (*fa/fa*), has a similar phenotype to *ob/ob* and *db/db* mice, as it has a homozygous missense mutation (*fatty*, *fa*) in the long form of the leptin receptor, which makes it insensitive to leptin [31,32]. Defects in the leptin receptor caused by this mutation result in the development of early-onset obesity due to hyperphagia, reducing the energy expenditure and leading to morbid obesity [14]. These rats are less likely to acquire diabetes, although ZFR has a high level of insulin resistance and fertility is reduced [14,20]

The ZFR is the most used model for studying several genetic characteristics associated with obesity [33,34], although it has also been used to study the anti-obesogenic effects of natural compounds such as the extracts of red wine [35], rosemary [36], green tea [37], bilberries, and purple potatoes [38] (Table 1).

2.4. Otsuka Long-Evans Tokushima Fatty Rat

The Otsuka Long-Evans Tokushima fatty (OLETF) rat is a spontaneous cholecystokinin type A (CCK-A) receptor knockout and does not respond to CCK, a peptide-derived hormone that functions as a peripheral satiety signal [20,39]. As a result, these rats are hyperphagic beginning several weeks after birth and develop mild obesity [34], which is a consequence of increased food intake and meal sizes, leading to an increase in body weight [40]. Moreover, OLETF rats develop diabetes, which manifests as polyuria and polydipsia [20]. At approximately 8 weeks of age, OLETF rats display hyperinsulinemia, and insulin resistance is observed at 12 weeks of age. Later, hyperplasia of pancreatic islets and hypertriglyceridemia develop [18].

The effects of gambigyeongsinhwan [41], gyeongshingangjeehwan [42], fermented mushroom milk-supplemented dietary fiber [43], or soy β-conglycinin [44] on obesity were evaluated in this animal model (Table 1).

2.5. Monosodium Glutamate (MSG)-Induced Obesity Model

The VMH nucleus, located in the hypothalamus, is associated with the regulation of eating behavior and satiety, with the use of rats with VMH lesions being one of the first models developed to induce obesity in rodents [14,20,45]. Bilateral lesions of the VMH nucleus lead to the development of hyperphagia, vagal hyperactivity, sympathetic hypoactivity, enlarged pancreatic islets, and hyperinsulinemia and can be caused by using the neurotoxin MSG [46,47]. MSG administration also causes lesions in the arcuate nucleus of the hypothalamus and circumventricular neurons. To induce obesity, MSG can be administered subcutaneously or intraperitoneally (2–4 mg/g of body weight) during the neonatal period, 4–10 times [48]. Adult rats who received MSG in the neonatal period developed endocrine dysfunction syndromes, which are characterized by obesity development, disturbances in the regulation of caloric balance, reduced growth, behavioral changes, and hypogonadism [47,49]. This obesity model was used to study the anti-obesogenic effects of Roselle (*Hibiscus sabdariffa* L.) [50] (Table 1).

Table 1. Anti-obesity effects of natural products in monogenic and neurotoxin monosodium glutamate (MSG)-induced obesity models.

Food Product/Plant	Bioactive Compounds	Strain/Obesity Model	Dose and Treatment	Observed Effects	References
Artemisia extract	Artemether	C57BL/KsJ *db/db* mice ♂	200 mg/kg (oral gavage), for 2 weeks	↓ Food intake and weight increase rate	[21]
				↓ Fasting blood glucose levels	
				↑ Tolerance to glucose	
				↑ Insulin sensitivity	
				↑ Insulin secretion	
				Improved hyperinsulinemia	
				Ameliorated islet vacuolar degeneration and hepatic steatosis	
				↓ Apoptosis of pancreatic beta cells	
Barley	N.A.	*db/db* mice (BKS.Cg-+*Lepr*^{db}/+*Lepr*^{db}/OlaHsd—fat, black, homozygous) ♂	88% (*w*/*w*; mixed with the diet), for 8 weeks	↓ Plasma insulin and resistin levels	[22]
				↓ TC levels in the liver	
Bilberries (*Vaccinium myrtillus*)	Nonacylated anthocyanin extract	Zucker (*fa/fa*) rats ♂, fed with HFD	25 mg/kg/day (oral gavage), for 8 weeks	↓ Fasting plasma glucose level	[38]
				↓ Levels of branched-chain amino acids	
				Improved lipid profiles	
Cannabis sativa	Cannabinoid Δ^9-tetrahydrocannabivarin	C57BL/6 *ob/ob* mice ♀	0.1, 0.5, 2.5 and 12.5 mg/kg/day (oral gavage), for 30 days	↓ Liver TG concentration (only for 12.5 mg/kg)	[27]
Cinnamon extract (*Cinnamomum zeylanicum*)	N.A.	B6.V-Lep^{ob}/J mice [on a C57BL/6J background (*ob/ob*)] ♂	4.5 mL/kg (equates to 0.8 g/kg) (in drinking water), for 6 weeks	↑ Insulin sensitivity and glucose tolerance	[28]
				↓ Hepatic levels of TG	
				↓ Fat accumulation in the liver	
				↑ Liver glycogen content	
				Improvement of insulin-stimulated locomotor activity	
Celastraceae family members (including *Tripterygium wilfordii*)	Celastrol (tripterine)	C57BL/6J *ob/ob* mice ♂, fed with HFD	3 mg/kg/day (mixed with the HFD), for 6 weeks	↓ B.w.	[30]
				↓ Liver weight	
				↓ TG levels in the liver	
				↑ Glucose clearance	
				Downregulation of intestinal lipid transporters	
				↑ Lipid excretion in feces	

Table 1. *Cont.*

Food Product/Plant	Bioactive Compounds	Strain/Obesity Model	Dose and Treatment	Observed Effects	References
Green tea	Polyphenols	Zucker (*fa/fa*) rats ♂, fed with HFD	200 mg/kg/day (oral gavage), for 8 weeks	↓ B.w. gain ↓ Visceral fat ↓ Fasting serum insulin, glucose and lipids levels	[37]
Liriope platyphylla (dry roots)	Aqueous extract	OLETF rats	5 or 10% (15 mL/g b.w./day; oral gavage), for 2 weeks	↓ Abdominal fat mass ↓ Glucose concentration ↑ Insulin production (only for 10% concentration) ↓ Expression of Glut-1	[51]
Mix of *Curcuma longa* L., *Alnus japonica* and Massa Medicata Fermentata	Gambigyeongsinhwan	OLETF rats ♂	250 or 500 mg/kg/day (oral gavage), for 8 weeks	↓ B.w. gain ↓ Adipose tissue weight and visceral adipocyte size ↑ mRNA levels PPARα in adipose tissue	[41]
Mix of edible mushrooms (*Lentinus edodes*, *Ganoderma lucidum*, *Pleurotus ostreatus* and *Flammulina velutipes*) in fermented milk	N.A.	OLETF rats ♂	10 and 20% (*v*/*w*; mixed with the diet), for 6 weeks	↓ B.w., ↓ Perirenal fat, visceral and epididymal fat (only for 20% concentration), ↓TG and FFA levels	[43]
Mix of *Liriope platyphylla*, *Platycodon grandiflorum*, *Schisandra chinensis*, and *Ephedra sinica*	Gyeongshingangjeehwan	OLETF rats ♂	121.7 mg/kg/day (oral gavage), for 8 weeks	↓ Visceral WAT weight ↓ Size adipocytes in mesenteric WAT ↓ mRNA expression levels of adipocyte marker genes (PPARγ, aP2 and leptin) in visceral WAT ↑ mRNA expression levels of PPARα target genes in visceral WAT ↓ Plasma levels of FFA, TG, insulin and glucose	[42]
Purple Potato *(Solanum tuberosum)*	Acylated anthocyanin extract	Zucker (*fa/fa*) rats ♂, fed with HFD	25 mg/kg/day (oral gavage), for 8 weeks	↓ Levels of branched-chain amino acids improved lipid profiles ↑ Glutamine/glutamate ratio ↓ Glycerol levels and metabolites involved in glycolysis	[38]
Red Wine (Provinols™)	Polyphenol extract (70% Polyphenols)	Zucker (*fa/fa*) rats	20 mg/kg/day (mixed with the diet), for 8 weeks	↓ Plasma levels of glucose, fructosamine, TG, TC and LDL-cholesterol ↑ NO ↑ eNOS activity ↓Superoxide anion	[35]

Table 1. *Cont.*

Food Product/Plant	Bioactive Compounds	Strain/Obesity Model	Dose and Treatment	Observed Effects	References
Roselle (*Hibiscus sabdariffa* L.) aqueous extract	Anthocyanins	Swiss Webster (CFW) mice ♂induced by MSG	120 mg/kg/day (60 mg/kg/day by oral gavage plus 60 mg/kg/day dissolved in tap water given *ad libitum*), for 60 days	↓ B.w. gain ↓ Glycemia ↑ ALT levels	[50]
Rosemary (*Rosmarinus officinalis* L.) extract	Carnosic acid and carnosol	Zucker (*fa/fa*) rats ♀	0.5% (*w*/*w*; mixed with the diet), for 64 days	↓ B.w. gain, ↓ Serum TG, TC and insulin levels Lipase activity inhibition in the stomach	[36]
Soy products, grains and legumes	Genistein	*ob/ob* mice ♀	0.06% (*w*/*w*; mixed with the diet), for 4 weeks	↓B.w. gain Downregulation of SOD activity ↑ iNOS expression in mesenteric artery perivascular adipose tissue	[25]

♂, male; ♀, female; ↓, decrease; ↑, increase; ALT, alanine aminotransferase; aP2, adipocyte fatty acid-binding protein; B.w., body weight; eNOS, endothelial nitric oxide-synthase; FFA, free fatty acids; Glut-1, glucose transporter 1; iNOS, inducible nitric oxide synthase; LDL, low density lipoprotein; MSG, monosodium glutamate; N.A., not applicable; NO, nitric oxide; PPAR-α, peroxisome proliferator-activated receptor alpha; PPARγ, peroxisome proliferator-activated receptor gamma; SOD, superoxide dismutase; TC, total cholesterol; TG, triglycerides; WAT, white adipose tissue; weeks, weeks.

2.6. Diet-Induced Obesity Models

Diet-induced obesity (DIO) rodent models are achieved by exposing rats and mice to specific diets that induce obesity, thereby reproducing dietary imbalances that are often the main cause of obesity in humans [13,20,52,53]. The main advantage of diets is that they can be standardized and control the nutrient percentages. There are a variety of diets that can be used for this purpose, such as high-fat diets (HFD), high-sugar diets (HSD), and high-sugar and high-fat (HSHF) diets, known as Western diets [16]. The HFD-induced obesity mouse model is one of the most used to understand the relationship between hyperlipidemic diets and the pathophysiology of obesity [52]. Within mouse strains, there are some more susceptible to DIO than others [13,54]; for example, the inbred C57BL/6 mouse strain is highly susceptible in contrast to SWR/J, A/J and CAST/Ei mouse strains, which tend to be resistant to these diets. In fact, the C57BL/6J mouse strain is the most used since when they are fed with HFD, these animals develop characteristics similar to humans with complex metabolic syndrome, such as obesity, high fat accumulation, insulin resistance, hyperglycemia, hyperlipidemia, hypertension, non-alcoholic fatty liver disease, and endothelium damage associated with cardiovascular diseases [18,20,52,55,56]. Some rat strains can also be used as models of HFD-induced obesity, such as the outbred Sprague Dawley, Wistar, or Long Evans rats [14]. However, Sprague Dawley rats showed diverse responses, with some animals showing DIO, while others showed resistance to the diet [13]. Detailed information on studies with natural compounds in HFD-induced obesity models is shown in Table 2.

Table 2. Effects of natural products on HFD-induced obesity models.

Food Product/Plant	Bioactive Compounds/Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Abeliophyllum distichum	N.A.	C57BL/6 mice ♂	100 and 300 mg/kg/day (oral administration), for 8 weeks	↓ B.w., ↓ Lipid accumulation (liver and BAT) ↓ Expression of lipogenic genes (PPARγ, C/EBPα, ACC, and FAS) (at 300 mg/kg). ↑ Expression of p-AMPK and p-ACC (at 300 mg/kg)	[57]
Acanthopanax senticosus	N.A.	C57BL/6J mice ♂	0.5 g/kg (oral administration), for 12 weeks	↓ B.w. gain ↓ Abdominal fat accumulation ↓ Liver TG accumulation ↓ LDL-cholesterol serum levels	[58]
Acanthopanax sessiliflorus	Saponins	ICR mice ♀	1% and 0.5% (*w*/*w*; mixed with the diet), for 4 weeks	↓ B.w.	[59]
American ginseng (*Panax quinquefolium*), stems and leaves	Saponins	ICR mice ♀	1% and 3% (*w*/*w*; mixed with the diet), for 8 weeks	↓ Adipose tissue weight ↓TG plasma levels	[60]
Balloon flower (Platycodon grandiflorum)	Water extract	Sprague Dawley rats ♂	150 mg/kg/day (oral administration), for 7 weeks	↓ B.w. gain ↓ Food intake ↓ Subcutaneous adipose tissue weight ↓ Subcutaneous adipocytes size ↓ TC and TG plasma levels	[61]
Bitter melon (*Momordica charantia* L.)	Ethanol extract	C57BL/6 mice ♂	250 and 500 mg/kg/day (mixed with the diet), for 12 weeks	↓ B.w. ↓ WAT weight ↑ Expression of SIRT-1 Suppressed PPARγ and SREBP-1 expressions of WAT	[62]
Blackcurrant (*Ribes nigrum*)	25% anthocyanins and 40% polyphenols	C57BL/6J mice ♂	0.1% (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w., ↓ Adipocyte size of the epididymal fat ↓ Inflammatory gene expression in the splenocytes (TNFα, IL-6, IL-1β) ↑ Gene expression in skeletal muscle (ACOX-1, PPARα, PPARδ, UCP-2, UCP-3, PGC-1α, TFAM)	[63]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Black tea extract	Polyphenol fraction	C57BL/6N mice ♀	5% of extract (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w., ↓ Parametrial adipose tissue ↓ Liver lipid content	[64]
Black wattle tree (*Acacia meansii*)	Acacia polyphenol	KKAy mice ♂	2.5% and 5% (*w*/*w*; mixed with the diet), for 7 weeks	↓ B.w. ↓ Glucose and insulin plasma levels ↓ mRNA expression of fat acid synthesis-related genes (SREBP-1c, ACC and FAS) in the liver ↓ mRNA expression of TNF-α in WAT ↑ mRNA expression of adiponectin in WAT ↑ mRNA expression of energy expenditure-related genes (PPARα, PPARδ, CPT1, ACOX and UCP-3) in skeletal muscle ↑ Protein expression of CPT1, ACOX and UCP-3	[65]
Broccoli florets and stalks (*Brassica oleracea* L. var. *italica*)	Aqueous extracts	Albino rats ♂	200 and 400 mg/kg/day (oral administration), for 1 month	↓ B.w. gain ↓ Adipose tissue index ↓ Serum levels of insulin, glucose, leptin, resistin and HOMA-IR index ↑ Adiponectin serum levels ↓ Serum levels of TC, TG and LDL-cholesterol ↑ HDL-cholesterol serum levels	[66]
	N.A.	C57BL/6J mice ♂	10% florets or 10% stalks (*w*/*w*; mixed with the diet), for 17 weeks	↓ Serum insulin levels and HOMA-IR index (only florets) ↑ Adiponectin receptors 1 and 2 mRNA expression (only florets)	[67]
Broccoli microgreens juice (*Brassica oleracea* L. var. *italica*)	N.A.	C57BL/6J mice ♂	20 g/kg/day (oral gavage), for 10 weeks	↓ B.w. ↓ WAT mass ↓ Liver fat ↓ Adipocyte size ↑ Water intake ↑ Glucose tolerance and insulin sensitivity ↓ Serum insulin levels, HOMA-IR index	[68]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
				↓ Serum levels of TG and LDL-cholesterol	
				↓ Serum levels of inflammatory cytokines (IL-1β, IL-6 and TNFα)	
Broccoli sprouts extract (*Brassica oleracea* L. var. *italica*)	Glucoraphanin-rich extract	C57BL/6JSlc mice ♂	0.3% (*w*/*w*; 2.2% extract powder mixed with the diet), for 14 weeks	↓ B.w. gain	[69]
				↓ Fat mass	
				↓ Liver weight	
				↓ Hepatic steatosis	
				↓ Hepatic oxidative stress	
				↑ Energy expenditure and core body temperature	
				↑ Glucose tolerance and insulin sensitivity	
				↓ Plasma insulin levels and HOMA-IR index	
				↑ Insulin stimulated Akt phosphorylation on Ser473 in the liver, quadriceps muscle and epididymal WAT	
				↑ UCP-1 protein levels in epididymal and inguinal WAT	
Brown alga (*Sargassum thunbergii)*	*Ethanol Extract*	C57BL/6 mice ♂	100 and 300 mg/kg/day (oral administration), for 7 weeks	↓ B.w.	[70]
				↓ WAT mass	
				↓ Occurrence of fatty liver	
				↓ Insulin, TG and TC serum levels	
				↓ Gene expression of PPARγ in WAT	
				↑ Expression of thermogenic genes (UCP-1 and UCP-3) in BAT	
Brown alga (Ecklonia cava)	N.A.	C57BL/6 mice ♂	5, 25 or 150 mg/kg/day (mixed with the diet), for 10 weeks	↓ B.w.	[71]
				↓ Liver weight,	
				↓ Epididymal, perirenal and mesenteric WAT	
				↓ Insulin, leptin and glutamate pyruvate transaminase serum levels	
				↓ Serum and hepatic levels of TG	
				↓ Hepatic protein expression levels of C/ERPα, PPARy, SREBP-1c, A-FABP, FAS and leptin	
				↑ Hepatic protein expression levels of GLUT4	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Brown alga Wakame (*Undaria pinnatifida*)	Fucoxanthin	C57BL/6J mice ♂	1.06% and 2.22% % (*w*/*w*; mixed with the diet), for 5 weeks	↓ B.w. ↓ WAT ↓ Plasma levels of insulin, glucose, leptin and LDL-cholesterol ↑ Plasma levels of TC ↓ mRNA expression of MCP-1 and leptin in WAT ↑ mRNA expression of Adrb3 in WAT ↑ mRNA expression of GLUT4 in skeletal muscle	[72]
Brown alga: *Undaria Pinnatifida* (UP), *Laminaria Japonica* (LJ), *Sargassum Fulvellum* (SF), Hizikia *Fusiforme* (HF)	N.A.	C57BL/6N mice ♂	5% of freeze-dried UP, LJ, SF, or HF (*w*/*w*; mixed with the diet), for 16 weeks	↓ Plasma levels of leptin ↓ Plasma levels of adiponectin (for UP supplementation) ↓ Formation of CLS in gonadal adipose tissue ↓ Insulin resistance (for LJ supplementation)	[73]
Cannabis sativa	Cannabinoid Δ^9-tetrahydrocannabivarin	C57BL/6 mice ♀	0.3, 1, 2.5, 5 and 12.5 mg/kg twice daily (oral gavage), for 30 days	↓ Glucose and insulin plasma levels for highest doses Improvement of insulin sensitivity index for highest doses.	[27]
Cauliflower mushroom (*Sparassis crispa*)	Lupane-type saponins	C57BL/6 mice ♂	1%, 3% and 5% (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w. gain ↓ Food intake ↓ FER ↓ Serum levels of TC and TG ↓ Liver lipids ↓ Occurrence of fatty liver deposits and steatosis	[74]
Chinese willow dry leaves (*Salix matsudana*)	Polyphenol fraction	ICR mice ♂	2% and 5% (*w*/*w*; mixed with the diet), for 9 weeks	↓ B.w. ↓ Parametrial adipose tissue ↓ Adipocyte size ↓ Hepatic TC (at 5% concentration)	[75]
Chitooligosaccharide	N.A.	C57BL/6N mice ♂	1% or 3% (*w*/*w*; mixed with the diet), for 5 months	↓ B.w. gain (at 3% concentration) ↓ Epididymal adipocyte size (at 3% concentration) ↓ Serum levels of TG and TC ↓ Hepatic levels of total lipid and TG (at 3% concentration) ↓ Serum levels of AST and ALT (at 3% concentration)	[76]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Chitosan and water-soluble derivatives chitosan oligosaccharides	N.A.	Sprague Dawley rat ♂	250, 500 and 1000 mg/kg × d (*w*/*w*; mixed with the diet), for 6 weeks	↓ B.w. gain ↓ Serum levels of LDL-cholesterol, TC and TG ↓ Hepatic levels of TC, TG and TBA ↑ Fecal levels of TC, TG and TBA ↓ ALT and AST levels in serum and liver ↑ SOD levels in serum and liver ↓ Growth inhibition of subcutaneous and mesenteric WAT Relieved fatty liver ↑ Liver mRNA expression of PPARα and HL	[77]
Chitosan (CTS) and water-soluble chitosan microspheres	N.A.	Sprague Dawley ♂	225 and 450 mg/kg/day (oral administration), for 4 weeks	↓ B.w. gain ↓ Blood lipids and plasma viscosity ↑ Serum levels of SOD	[78]
Clusia nemorosa L.	Betulinic acid	Swiss mice ♂	50 mg/L (in drinking water), for 15 weeks	↓ B.w. ↓ Abdominal fat accumulation ↓ Plasma levels of glucose, TG and TC ↑ Plasma levels of insulin and leptin ↓ Plasma levels of amylase and ghrelin	[79]
Cocoa powder (*Theobroma cacao* L.)	Cocoa polyphenol extract	C57BL/6N mice ♂	40 and 200 mg/kg (mixed with the diet), for 5 weeks	↓ B.w. gain ↓ Fat accumulation	[80]
Common bean dried (*Phaseolus vulgaris* L.)	N.A.	C57BL/6J mice ♂	30% and 46.5% (*w*/*w*; mixed with the diet), for 7 or 12 days, respectively	↓ B.w. and Lee Index ↓ Plasma levels of TG, LDL-cholesterol	[81]
Cornelian cherries (*Cornus mas*)	Anthocyanins	C57BL/6 mice ♂	1 g/kg (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w., Improvement of glucose tolerance ↓ Lipid accumulation in liver ↑ Plasma insulin levels	[82]
	Ursolic acid	C57BL/6 mice ♂	500 mg/kg (*w*/*w*; mixed with the diet), for 8 weeks	Improvement of glucose tolerance ↓ Lipid accumulation in liver ↑ Plasma insulin levels	[82]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Cudrania tricuspidata fruits	6,8-diprenylgenistein (DPG) (a major isoflavonoid)	C57BL/6J mice ♂	10 and 30 mg/mL (in distilled water) (oral administration of 10 mL/kg), for 6 weeks	↓ B.w. gain ↓ FER ↓ Epididymal fat weight ↓ Epididymal adipocyte size ↓ Liver fat accumulation and weight ↓ Serum levels of TC, TG, HDL-cholesterol, LDL-cholesterol, ALT and AST ↓ Protein levels of PPARγ, C/EBPα and leptin in adipose tissue ↑ Protein levels of adiponectin in adipose tissue ↑ Phosphorylation of AMPK and ACC	[83]
Curcumin (*Curcuma longa*)	Curcuminoids	Sprague Dawley rat ♂	0.2% and 1% (*w*/*w*; mixed with the diet), for 2 weeks	↓ Epididymal adipose tissue weight ↓ Hepatic levels of TC and TG (at 1% concentration) ↑ Hepatic ACOX activity	[84]
	N.A.	C57BL/6 mice ♂	500 mg/kg (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w. gain and body fat ↓ Liver weight and hepatic steatosis ↓ TC serum levels ↓ mRNA expression of VEGF and VEGFR-2 in adipose tissue ↓ Microvessel density in adipose tissue ↑ Phosphorylation of AMPK and ACC in adipose tissue ↑ mRNA expression of CPT-1 in adipose tissue ↓ mRNA expression of GPAT-1 in adipose tissue ↓ mRNA expression of PPARγ and C/EBPα in adipose tissue	[85]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Dioscorea nipponica Makino	Methanol extract	Sprague Dawley ♂	2% or 5% (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w. gain ↓ Subcutaneous, perirenal and epididymal fat ↓ Plasma levels of TG, TC, VLDL-cholesterol and atherogenic index ↑ HDL-cholesterol plasma levels ↑ Fecal fat excretion	[86]
Dioscorea oppositifolia	n-BuOH extract of *D. oppositifolia*	ICR mice ♀	100 mg/kg (oral administration), for 8 weeks	↓ B.w. gain ↓ FER ↓ Parametrial adipose tissue weight ↓ Liver weight ↓ Serum levels of TG, TC LDL-cholesterol and atherogenic index ↑ HDL (in serum) ↓ Hepatic levels of total lipids, TG, TC, AST and ALT ↑ Fecal excretion of TG, TC and total lipids	[87]
Fig fruit (*Ficus carica* L.)	Aqueous-ethanolic extract	Wistar male ♂	400 mg/kg (*w*/*w*; mixed with the diet), for 8 weeks	↓ Plasma levels of TC, TG and LDL-cholesterol ↑ HDL-cholesterol plasma levels ↓ TBARS levels in liver, kidney and heart ↑ Antioxidant enzymes (GPx, SOD and CAT) in liver, kidney and heart	[88]
Fraxinus excelsior L. seed extract (FraxiPure™)	1 phenolic compound, and 9 secoiridoid glucosides	C57BL/6J mice ♂	0.5% (*w*/*w*; mixed with the diet), for 16 weeks	↓ B.w. gain ↓ omental and retroperitoneal fat ↓ fasting blood glucose levels and plasma insulin levels ↓ Liver weight gain and incidence of fatty liver	[89]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Galangal (*Alpinia officinarum* Hance)	Ethanolic extract	Sprague Dawley ♂	3% and 5% (*w*/*w*; mixed with the diet), for 6 weeks	↓ B.w. gain	[90]
				↓ FER	
				↓ Adipose tissue weight	
				↓ Serum levels of TC, TG, LDL-cholesterol, atherogenic index, leptin and ALT	
				↑ HDL-cholesterol serum levels	
				↓ Hepatic levels of TC and TG	
Garlic (*Allium sativum* L.)	Chlorophyll, carotenoids and vitamin C	C57BL/6J mice ♂	100, 250 and 500 mg/kg/day (oral administration), for 4 weeks	↓ B.w. gain	[91]
				↓ FER	
				↓ WAT weight and adipocyte size	
				↓ Serum levels of TC, TG and leptin	
				↓ Serum levels of fasting glucose, insulin and HOMA-IR	
				↑ Serum levels of high-molecular-weight adiponectin	
				↓ Hepatic levels of TC and TG	
				↑ Fecal TG excretion	
				↓ Hepatic FAS levels	
				↑ Hepatic CPT-1A levels	
				↓ HMG-CoA reductase activity	
				↑ Hepatic antioxidant enzyme activities (SOD, GST, GSH, GPx and GR)	
				↓ Hepatic MDA activity	
Ginger rhizomes (*Zingiber officinale Roscoe*)	N.A.	C57BL/6J mice ♂	500 mg/kg/day (oral gavage), for 16 weeks	↓ B.w.	[92]
				↓ Fat accumulation	
				↓ Serum levels of glucose, TG and TC	
				Enhancement of BAT function and activation of WAT browning	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Ginseng (*Panax ginseng*)	Saponins	Balb/c ♂mice	3% (*w*/*w*; mixed with the diet), for 3 weeks	↓ B.w. ↓ FER ↓ TG plasma levels	[93]
	N.A.	C57BL/6J mice ♂	0.5 g/kg (*w*/*w*; mixed with the diet), for 15 weeks	↓ Body fat mass, ↑ Glucose tolerance and insulin sensitivity ↓ Plasma levels of TG, HDL-cholesterol, insulin and leptin ↑ Body temperature Prevented hypertension ↑ Fatty acid oxidation in liver ↑ mRNA expression of C/EBPa, PPARγ and FAS in adipose tissue	[94]
Golden mushroom (*Pleurotus citrinopileatus*)	Water extract	C57BL/6J mice ♂	400 and 800 mg/kg/day (oral gavage), for 12 weeks	↓ B.w. gain ↓ Food intake ↓ Fat accumulation ↑ Glucose tolerance ↓ Serum levels of TG, TC, LDL-cholesterol, AST, nonesterified fatty acid and creatinine ↑ HDL-cholesterol serum levels	[95]
Grape skin extract (*Vitis aestivalis*)	Phenolic compounds	C57BLK/6J mice ♂	250 mg/kg/day (mixed with the diet), for 12 weeks	↑ B.w. ↓ Fasting blood glucose and plasma CRP levels	[96]
Green alga (*Caulerpa okamurae*)	Ethanolic extract	C57BL/6 mice ♂	250 mg/kg (oral gavage), for 10 weeks	↓ B.w., ↓ Fat weight ↓ Liver weight ↓ Plasma levels of FFA, TG, TC, glucose and insulin ↓ Hepatic levels of FFA, TG, TC, and total lipid ↓ PPARγ and C/EBPα protein levels in adipose tissue ↓ mRNA expression of FAS, SREBP-1c, ACC, and CD36 in adipose tissue	[97]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Green alga (*Codium fragile*)	*Ethanol Extract*	C57BL/6 mice ♂	600 mg/kg/day (intragastric administration), for 12 weeks	↓ B.w.,	[98]
				↓ Size of adipocytes	
				↓ Serum levels of TC and glucose	
				↑ Abundance of Bacteroidetes species in the gut	
				↓ Abundance of Verrucomicrobia species in the gut	
Gymnema sylvestre	Methanol extract	C57BL/6 mice ♂	1 g/kg (*w*/*w*; mixed with the diet), for 4 weeks	↓ B.w.	[99]
				↓ Abdominal and epididymal fat weight	
				↓ Serum levels of TC, TG, LDL-cholesterol, VLDL-cholesterol, leptin, AST and ALT	
				↓ Occurrence of hepatic steatosis	
Halophyte (*Nitraria retusa*)	Ethanol extract	C57BL/6 mice ♂	50 and 100 mg/kg/day (oral administration), for 4 weeks	↓ B.w. gain	[100]
				↓ FER	
				↓ Adipose tissue weight	
				↓ Serum levels of TG and glucose	
				↑ HDL-cholesterol	
				↑ Hepatic mRNA expression of PPARγ1, PPARα, ACC-1, CPT1 and LPL	
				↓ Hepatic mRNA expression of FAS	
Indian lotus leaves extract (*Nelumbo nucifera* Gaertn.)	Alcoholic extract	ICR mice ♀	5% (*w*/*w*; mixed with the diet), for 5 weeks	↓ B.w.	[101]
				↓ Parametrial adipose tissue weight	
				↓ Hepatic TG levels	
Indian lotus (*Nelumbo nucifera*) and Peach tree (*Prunus persica*) *mixture*	N.A.	C57BL/6 mice ♂	0.1%, 0.2% and 0.4% (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w. gain	[102]
				↓ Abdominal fat weight	
				↓ Liver weight	
				↓ Hepatic levels of TG and TC	
				↓ Serum levels of glucose, TC, ALT, AST and leptin	
				↑ Adiponectin serum levels	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
				↑ AST/ALT and adiponectin/leptin ratios	
				↓ mRNA levels of FAS and SCD-1 in adipose tissue (at 0.4% concentration)	
				↑ mRNA levels of PGC-1a and PPARα in adipose tissue (at 0.4% concentration)	
Japanese Horse Chestnut (*Aesculus turbinata* BLUME)	Escins (saponin)	ICR mice ♀	0.35%, 1% and 2% (*w*/*w*; mixed with the diet), for 11 weeks	↓ Parametrial adipose tissue (at 2% concentration)	[103]
				↓ Hepatic levels of TG	
				↑ TG fecal excretion (at 2% concentration)	
	Saponins	ICR mice ♀	0.1% and 0.5% (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w.	[104]
				↓ Peritoneal adipose tissues	
				↓ TG plasma levels	
				↓ GOT activity	
				↑ TG fecal excretion	
Konjac (*Amorphophallus konjac*)	Liquid konjac	C57BL/6J mice ♂	2.5% and 5% (*w*/*w*; mixed with the diet), for 80 days	↓ B.w. gain	[105]
				↓ FER	
				↓ Abdominal fat accumulation	
				↓ Liver weight	
				↓ Serum levels of TC, leptin, insulin and HOMA-IR	
				↓ Hepatic levels of TC and TG	
				↑ Fecal fat excretion	
Korean red ginseng (*Ginseng Radix Rubra*)	Crude saponin	Sprague Dawley rats ♂	200 mg/kg/day (intraperitoneal administration), for 3 weeks	↓ B.w.	[106]
				↓ Food intake	
				↓ Fat weight	
				↓ Serum leptin levels	
				↓ Expression of NPY neurons in the hypothalamus	
Lacquer tree leaf extract (*Rhus verniciflua*)	Quercetin	C57BL/6 mice ♂	1% and 2% (*w*/*w*; mixed with the diet), for 56 days	↓ B.w.	[107]
				↓ Intra-abdominal fat	
				↓ Plasma leptin levels	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Lemon balm (*Melissa officinalis*)	Ethanol extract	C57BL/6J mice ♂	200 mg/kg/day (in drinking water), for 6 weeks	↓ Hyperglycemia and insulin resistance ↓ Plasma levels of TG, nonesterified fatty acids and LDL/VLDL cholesterol ratio ↑ HDL/LDL cholesterol ratio hyperglycemia and insulin resistance, hyperglycemia and insulin resistance, hyperglycemia and insulin resistance	[108]
Milk thistle seeds extract (*Silybum marianum*)	Silibinin	C57BL/6 mice ♂	50 mg/kg (intraperitoneal injection), for 8 weeks	↓ B.w. gain ↓ Fat accumulation in liver ↓ Fat accumulation and adipose tissue hypertrophy Reversed gene expression profile from pro-inflammatory to anti-inflammatory profile	[109]
Moringa oleifera L.	N.A.	C57BL/6J mice ♂	250 mg/kg/day (oral administration), for 10 weeks	↓ Liver weight and hepatic lipid accumulation ↑ Glucose tolerance ↓ Oxidative stress, endoplasmic reticulum stress and lipotoxicity in quadriceps muscles ↓ Hepatic expression of genes involved in lipid synthesis (ACC, FAS, LPL and SREBP-1c) ↑ Hepatic genes involved in lipid oxidation (CD36 and ATGL) ↓ Proinflammatory cytokine mRNA expression (TNF-α, IL-1β, IL-6, IL-12 and MCP-1) in the liver, epididymal adipose tissue, and quadriceps	[110]
	Ethanolic extract	Wistar rats ♀	600 mg/kg/day (oral administration), for 12 weeks	↓ B.w., Improvement of the atherogenic index and coronary artery index ↓ Serum glucose levels and insulin resistance ↓ mRNA expression of leptin and resistin in adipose tissue ↑ mRNA expression of adiponectin in adipose tissue ↓ Hepatic levels of AST and ALT	[111]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Muscadine wine phytochemical and muscadine grape phytochemical (*Vitis rotundifolia*)	Anthocyanins	C57BL/6J mice ♂	0.4% (*w*/*w*; mixed with the diet) of each phytochemical, for 15 weeks	↓ B.w. ↑ Glucose tolerance ↓ Plasma levels of FFA, TG, TC, CRP	[112]
Mushroom (*Ganoderma lucidum*)	Ethanolic extract	Specific pathogen free (SPF) C57BL/6 mice ♂	1%, 3% or 5% (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w. gain ↓ FER ↓ WAT weight ↓ Size of adipocytes in epididymal WAT ↓ Liver weight ↓ Serum levels of TG, TC, HDL-cholesterol, LDL-cholesterol and FFA ↓ Serum levels of glucose, insulin and leptin ↑ Serum adiponectin levels ↑ Glucose tolerance and insulin sensitivity ↓ mRNA expression of lipogenic genes (FAS, SCD1 and SREBP-1c) in liver and WAT	[113]
	Water extract	C57BL/6NCrlBltw ♂	2%, 4% and 8% (*w*/*v*; oral gavage of 100 µL, daily), for 8 weeks	↓ B.w., ↓ Epididymal and subcutaneous fat ↓ Liver weight ↓ mRNA expression levels pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and PAI-1) in the liver and adipose tissues ↑ mRNA expression levels of IL-10 in the liver and adipose tissues	[114]
Mushroom (*Mycoleptodonoides aitchisonii*)	N.A.	C57BL/6 mice ♂	1%, 3% and 5% (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w. gain ↓ Food intake ↓ FER ↓ Adipose tissue weight ↓ Serum levels of TC and TG ↓ Hepatic lipid and TC levels ↓ Occurrence of fatty liver deposits and steatosis ↓ Epididymal adipocyte size	[115]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Mushroom (*Pleurotus citrinopileatus*)	Ethanolic extract	C57BL/6J mice ♂	200 and 500 mg/kg, for 12 weeks	↓ B.w. gain ↓ Fat accumulation ↑ Glucose tolerance	[116]
Oiltea camellia	Ethanolic extract	ICR mice ♀	100, 200 and 300 mg/kg (oral administration), for 4 weeks	↓ B.w. ↓ Fat accumulation ↓ Serum levels of TC and TG ↑ HDL-cholesterol serum levels ↓ Hepatic FAS activity	[117]
Olive leaf extract (*Olea europaea* L.)	Ethanolic extract	C57BL/6N mice ♂	0.15% (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w. gain ↓ Food intake ↓ FER ↓ Visceral fat-pad weights ↓ Plasma levels of glucose and leptin ↓ Plasma levels of TG, TC, LDL + VLDL cholesterol and FFA ↓ Gene expression of PPARγ, C/EBPα, CD36, FAS, and leptin in the epididymal adipose tissue	[118]
Oolong tea dry leaf (*Thea sinensis* L.)	Caffeine	ICR mice ♀	5% (*w*/*w*; mixed with the diet), for 10 weeks	↓ B.w. ↓ Parametrial adipose tissue ↓ Accumulation of liver TG	[119]
Panax japonicus rhizomes	Chikusetsusaponins	ICR mice ♀	1% and 3% (*w*/*w*; mixed with the diet), for 9 weeks	↓ B.w. ↓ Parametrial adipose tissue weight ↓ Liver weight ↓ Hepatic TG levels ↑ Feces weight and TG fecal excretion	[120]
Perilla leaf extract (*Perilla frutescens* L.)	Ethanolic extract	C57BL/6 mice ♀	1% and 3% (*w*/*w*; mixed with the diet), for 4 weeks	↓ B.w. gain ↓ FER ↓ Epididymal fat mass ↓ Liver weight	[121]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
				↓ Occurrence of hepatic steatosis	
				↓ Plasma levels of TG, TC and LDL-cholesterol	
				↑ HDL-cholesterol plasma levels	
				↓ Gene expression of ACC, GPDH and PPARγ in epididymal adipose tissue	
Platycodi radix (*Platycodon grandiflorum*)	Saponins	ICR mice ♀	5% (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w.,	[122]
				↓ Parametrial adipose tissue weight	
				↓ Hepatic TG levels	
Pomegranate leaf extract (*Punica granatum*)	10.6% ellagic acid	ICR mice ♀and ♂	400 and 800 mg/kg/day (oral gavage), for 5 weeks	↓ B.w.	[123]
				↓ Energy intake	
				↓ Adipose pad weight percents and Lee index	
				↓ Serum levels of glucose, TC, TG and TC/HDL-cholesterol ratio	
Ramulus mori (the twig of *Morus alba* L.)	Ethanolic extract	C57BL/6 mice ♂	20, 50 and 100 mg/kg/day (oral administration), for 7 weeks	↓ B.w.	[124]
				↓ Epididymal adipose tissue weight	
				↓ Liver weight	
				↓ Lipid accumulation in the liver	
				↓ Serum levels of TC and TG	
				↓ mRNA expression and protein levels of PPARγ, C/EBPα, SREBP-1, ACC, FAS and SCD-1	
				↑ mRNA expression and protein levels of lipolytic genes (ATGL and HSL)	
Red alga (*Gelidium amansii*)	70% ethanol extract	C57BL/6 mice ♂	1% and 3% (*w*/*w*; mixed with the diet), for 12 weeks	↓ B.w.	[125]
				↑ Food and water intake	
				↓ Epididymal fat weight	
				↓ Serum levels of TC, TG, glucose and insulin	
	Ethanolic extract	C57BL/6J mice ♂	0.5%, 1% and 2% (*w*/*w*; mixed with the diet), for 8 weeks	↓ B.w.	[126]
				↓ Epididymal and mesenteric adipose tissue weight	
				↓ Liver weight	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
				↓ Plasma levels of TC, TG, LDL-cholesterol, FFA, and leptin	
				↑ Plasma levels of HDL-cholesterol and adiponectin	
				↓ Hepatic TC and TG levels	
				↓ Protein expression of FAS, SREBP-1c, PPARγ, and C/EBPα	
				↑ Protein expression of HSL and p-AMPK	
Red wine	2.09 g/L total polyphenol	Zucker lean rats ♂	Free access to red table wine (average consumption of 1.70 ± 0.38 mL/day per animal, corresponding to a dose of 3.4 ± 0.79 mg/day per animal of total polyphenols)	↓ B.w. gain	[127]
				↓ Energy intake	
				↓ Epididymal fat weight	
Roselle (*Hibiscus sabdariffa* L.)	Anthocyanins (delphinidin-3-sambubioside and cyanidin-3-sambubioside)	C57BL/6NHsd mice ♂	33 mg/kg (oral gavage) three times a week, for 8 weeks	↓ B.w. gain	[128]
				↓ WAT accumulation	
				↓ Serum levels of TG, LDL-cholesterol and glucose	
				↑ HDL-cholesterol serum levels	
				↓ Hepatic steatosis	
				↓ Hepatic mRNA levels of SREBP-1c, PPARγ, TNF-α and IL-1	
				↑ Hepatic CAT mRNA expression	
Safflower (*Carthamus tinctorius* L.)	Safflower yellow (SY) and hydroxysafflor yellow A (HSYA)	C57BL/6 mice ♂	200 mg/kg/day SY or HSYA (intraperitoneal injection), for 10 weeks	↓ B.w.	[129]
				↓ WAT mass	
				↓ Blood glucose levels and HOMA-IR	
				↓ Serum ALT levels	
				↑ Hepatic SOD activity	
				↑ mRNA levels of antioxidant enzymes in liver and epididymal adipose tissues	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
Salvia plebeian	Ethanolic extract	C57BL/6 mice ♂	200 and 400 mg/kg/day (oral administration), for 8 weeks	↓ B.w. ↓ Adipose tissue weight ↓ Liver weight ↓ Hepatic steatosis, TG accumulation and inflammatory cells infiltration ↓ Serum levels of TG, HDL-cholesterol, leptin, adiponectin and glucose ↓ Adipocytes size in adipose tissue ↓ Expression of adipogenesis transcription factors and lipogenesis-related target genes in adipose tissue	[130]
Soybean (*Glycine max* (L.) *Merrill*)	Ethanolic extract (soyasaponin Ab)	C57BL/6 mice ♂	15 and 45 mg/10 mL/kg/day (oral administration), for 10 weeks	↓ B.w. ↓ Adipose tissue weight ↓ Liver weight and steatosis ↓ Serum levels of TC, TG, FFA, LDL-cholesterol, AST and ALT ↓ Hepatic lipid synthesis (SREBP1c) ↑ Hepatic fatty acid oxidation (p-AMPKα, PPARα, PGC1α, and ACOX) and lipid export (MTTP and ApoB) ↓ Expression of inflammatory genes (TNFα, IL-6, IL-1β, iNOS, COX2, CD14 and F4/80) in liver ↓ WAT differentiation and lipogenesis (PPARγ, C/EBPα, and FAS) ↑ Browning genes (PGC1α, PRDM16, CIDEA, and UCP1) in adipose tissue	[131]
Wasabi leaf (*Wasabia japonica* Matsum.)	Water extract	C57J/BL mice ♂	5% (*w*/*w*; mixed with the diet), for 163 days	↓ B.w. gain ↓ Liver weight ↓ Epididymal WAT ↓ Plasma levels of TC, leptin and γ-GTP	[132]

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
				↓ Gene expression of PPARγ, leptin and C/EBPα in WAT	
				↑ Gene expression of adiponectin and ACOX1 in WAT	
				↓ Gene expression of PPARγ, SREBP-1c, ACC1, FAS and HMG-CoA reductase in liver	
				↑ PPARα gene expression in liver	
White mushroom exoskeleton (*Agaricus bisporus*)	Chitosan	C57BL/6J mice ♂	5% (*w*/*w*; mixed with the diet), for 10 weeks	↓ B.w. gain	[133]
				↓ FER	
				↓ Adipose tissue weight	
				↓ Fat accumulation in liver and muscle	
				↓ TG levels in serum, liver and muscle	
				↓ TC levels in serum and muscle	
				↓ Serum levels of IL-6, leptin, resistin, insulin	
				↓ FIAF mRNA expression in visceral adipose tissue	
				↑ Caecal tissue weight and content weight	
				↑ Caecal total lipids and nonesterified fatty acid levels	
				↑ β-hydroxybutyrate plasma levels in postprandial state	
Yeast (*Saccharomyces cerevisiae*)-fermented aged black garlic	N.A.	ICR mice ♀	100, 200 and 400 mg/kg (10 mL/kg; oral administration), for 63 days	↓ B.w.	[134]
				↓ Adipose tissue accumulation and adipocytes diameter	
				↓ Serum levels of TC, TG, LDL-cholesterol, AST, ALT, BUN and creatinine	
				↑ HDL-cholesterol serum levels	
				↓ Hepatic steatosis and hepatocyte hypertrophy	
				↓ Number of abnormal kidney tubules	
Yerba maté extract (*Ilex paraguariensis*)	Water extract	Swiss mice ♂	1 g/kg (oral gavage), for 8 weeks	↓ B.w.	[135]
				↓ Epididymal fat weight	
				↓ Serum levels of TC, TG, LDL-cholesterol and glucose	
				↓ Expression levels of cytokines (TNF-α, IL-6 and leptin) and chemoattractant proteins (CCR2 and CCL2) in WAT	

Table 2. *Cont.*

Food Product/Plant	Bioactive Compounds/ Extraction Method	Strain	Dose and Treatment	Observed Effects	Reference
				↓ Expression of genes involved in the regulation of blood pressure, vascular homeostasis or angiogenesis (angiotensinogen and PAI-1) in WAT	
				↑ Expression of genes involved in adipogenesis (PPARγ) and glucose and lipid metabolism (adiponectin) in WAT	
				↑ Expression of genes implicated in thermogenesis (PGC-1α and UCP-1) in BAT	
				↓ Macrophage infiltration marker (F4/80) in epididymal fat	

♂, male; ♀, female; ↓, decrease; ↑, increase; ACC, acetyl-CoA carboxylase; ACOX-1, acyl-CoA oxidase 1; Adrb3, β3-adrenergic receptor; A-FABP, adipose fatty acid-binding protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; aP2, adipocyte fatty acid-binding protein; ApoB, apolipoprotein B; ATGL, adipose triglyceride lipase; BAT, brown adipose tissue; B.w., body weight; BUN, blood urea nitrogen; CAT, catalase; CCL2, C-C motif chemokine ligand2; CCR2, CCL receptor 2; CD14, cluster of differentiation 14; CD36, cluster of differentiation 36; C/EBPα, CCAAT/enhancer binding protein alpha; CIDEA, cell death-inducing DNA fragmentation factor-like effector A; CLS, crown-like structures; CPT1, carnitine palmitoyl-transferase 1; CRP, C-reactive protein; eNOS, endothelial nitric oxide-synthase; FAS, fatty acid synthase; FER, food efficiency ratio; FFA, free fatty acids; FIAF, fasting-induced adipose factor; γ-GTP, gamma-glutamyltranspeptidase; GLUT4, glucose transporter type 4; GOT, glutamic oxaloacetic transaminase; GPAT-1, glycerol-3-phosphate acyl transferase 1; GPDH, glycerol-3-phosphate dehydrogenase; GPx, glutathione peroxidase; GR, glutathione reductase; GSH, glutathione; GST, glutathione S-transferase; HDL, high-density lipoprotein; HL, hepatic lipase; HMG-CoA reductase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; HOMA-IR, homeostatic model assessment for insulin resistance; HSL, hormone-sensitive lipase; IL-1β, interleukin 1 beta; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; LDL, low density lipoprotein; LPL, lipoprotein lipase; MCP-1, monocyte chemoattractant protein 1; MDA, malondialdehyde; MSG, monosodium glutamate; MTTP, microsomal triglyceride transfer protein; N.A., not applicable; NO, nitric oxide; NPY, neuropeptide Y; p-ACC, phosphorylated ACC; PAI-1, plasminogen activator inhibitor 1; p-AMPK, phosphorylated adenosine monophosphate-activated protein kinase; PGC-1α, PPARγ coactivator 1 alpha; PPAR-α, peroxisome proliferator-activated receptor alpha; PPARδ, peroxisome proliferator-activated receptor delta; PPARγ, peroxisome proliferator-activated receptor gamma; PRDM16, PR domain containing 16; SCD-1, stearoyl-CoA desaturase-1; SIRT1, Sirtuin 1; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein 1c; TBA, total bile acid; TBARS, thiobarbituric acid reacting substances; TC, total cholesterol; TFAM, mitochondrial transcription factor A; TG, triglycerides; TNFα, tumor necrosis factor alpha; UCP-1, uncoupling protein 1; UCP-2, uncoupling protein 2; UCP-3, uncoupling protein 3; VEGF, vascular endothelial growth factor; VEGFR-2, VEGF receptor 2; VLDL, very low density lipoprotein; WAT, white adipose tissue; weeks, weeks.

3. Conclusions

Within the various models of obesity in rodents, HFD-induced obesity is one of the most used to study the potential benefits of compounds of natural origin in the obesity disease, as it best simulates the development of obesity in humans. Furthermore, depending on the stability of the compound, the administration of substances through their incorporation into the diet facilitates administration to animals while simulating the natural humans' intake, the oral route. This is important because a practical way to ingest these natural compounds with anti-obesogenic properties can be through their incorporation into functional foods. There is no ideal rodent obesity model that can recap all the underlying mechanisms of obesity. Each model has advantages and disadvantages. Depending on the research objective, costs, and available model, researchers should select the option that best suits their needs. The translation and application of the results obtained from animal models of obesity, treated with potential therapeutic natural compounds, to humans are of great importance, as this can contribute to the resolution of this public health problem with theoretically minor adverse effects. However, this translation of knowledge has its limitations. For example, despite the physiological similarities, the metabolism between rodents and humans is different, which also translates into different effective doses. The same can also apply to the potentially toxic effects of a particular compound. Furthermore, it is difficult to mimic human disease in a given animal model, and doses and administration protocols are often not comparable. However, it is undeniable that the translation of knowledge from animal models to humans has been a very useful tool, allowing the testing of new pharmacological and therapeutic agents to respond to various human diseases.

Author Contributions: Conceptualization, T.M., T.F., E.N.-G., C.C.-R., S.L., E.R., L.M.A. and P.A.O.; writing—original draft preparation, T.M., T.F., E.N.-G., C.C.-R. and S.L.; writing—review and editing, T.M., T.F., E.N.-G., C.C.-R., S.L., L.M.A. and P.A.O.; supervision, L.M.A. and P.A.O.; funding acquisition, E.R. All authors have read and agreed to the published version of the manuscript.

Funding: This work was funded by the Portuguese Foundation for Science and Technology (FCT) and co-financed by the European Regional Development Fund (FEDER) through COMPETE 2020—Operational Competitiveness and Internationalization Programme (POCI), grant PTDC/ASP-HOR/29152/2017, POCI-01-0145-FEDER-029152 (VALORIZEBYPRODUCTS). This work was also supported by National Funds by FCT—Portuguese Foundation for Science and Technology, under the project UIDB/04033/2020. The authors acknowledge the financial support provided by the Portuguese Foundation for Science and Technology (FCT) through a Doctoral Grant (2020.04789.BD, Tiago Ferreira and BD/136747/2018, Elisabete Nascimento-Gonçalves).

Conflicts of Interest: The authors declare no conflict of interest.

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