Obesity Treating Natural Products

Subjects: Pharmacology & Pharmacy | Food Science & Technology | Integrative & Complementary Medicine
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Obesity is a global issue faced by many individuals worldwide. However, no drug has a pronounced effect with few side effects. Green tea, a well-known natural product, shows preventive effects against obesity by decreasing lipogenesis and increasing fat oxidation and antioxidant capacity. In contrast, other natural products are known to contribute to obesity. The natural products were classified as single compounds, foods, teas, fruits, herbal medicines—single extract, herbal medicines—decoction, and herbal medicines—external preparation. Then, the mechanisms of these medicines were organized into lipid metabolism, anti-inflammation, antioxidation, appetite loss, and thermogenesis. This research aimed to assess the efficacy and mechanisms of effective natural products in managing obesity. Several clinical studies reported that natural products showed antiobesity effects, including *Coffea arabica* (coffee), *Camellia sinensis* (green tea), *Caulerpa racemosa* (green algae), *Allium sativum* (garlic), combined *Ephedra intermedia* Schrenk, *Thea sinensis* L., and *Atractylodes lancea* DC extract (known as Gambisan), *Ephedra sinica* Stapf, Angelica Gigantis Radix, Atractylodis Rhizoma Alba, *Coicis semen*, *Cinnamomi cortex*, *Paeoniae radix*alba, and *Glycyrrhiza uralensis* (known as Euiiyin-tang formula).

obesity natural products lipid metabolism metabolic syndrome lipid metabolism antioxidant anti-inflammation

1. Introduction

Obesity is an excessive accumulation of fat, which poses a potential health risk. Specifically, a body mass index (BMI) of >30 is considered obese [1][2]. Currently, >1 billion individuals are obese globally [3]. This number is still increasing [3], meaning that an increasing number of individuals are becoming susceptible to many serious diseases, such as hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, osteoarthritis, and cancer, due to this chronic and relapsing disease [4].

One typical treatment for obesity is weight loss drugs approved by the US Food and Drug Administration, including orlistat, phentermine-topiramate, and naltrexone-bupropion. Chemical medications can help lose weight and maintain weight loss but can also cause changes in behavior [5]. However, weight-loss drugs have been withdrawn from the market because of side effects [6]. Among those still in use, orlistat, naltrexone-bupropion, phentermine-topiramate, liraglutide, and semaglutide have been used for long-term treatment. In contrast, others are only used for short-term treatment due to unguaranteed safety over longer periods [5]. Even these drugs may show adverse effects in some individuals and can be inaccessible because of high prices [6].

Therefore, developing new drugs, including botanical drugs, phytomedicines, traditional medicines, and herbal medicines, has gained importance. They have been suggested as substitutes for chemical drugs to reduce side effects while maintaining effectiveness. For example, *Ephedrae herba* showed preventive effects against hyperlipidemia in mice, possibly by regulating DNA repair and modulating the expression of genes and proteins related to energy metabolism [7].

2. Obesity Treating Natural Products

2.1. Single Compound

One study with a single compound showed antiobesity effects (**Table 1**). Diethyl azelate (DEA) is naturally produced in animals and plants and can be used to improve related metabolic syndromes [8]. Steeper et al. reported that daily oral DEA decreased total cholesterol (TC) and low-density lipoprotein (LDL) levels in human males who were overweight, alleviating obesity. This study on DEA included 17 participants and lasted for 21 days. More reliable results would have been drawn if this study had enrolled more subjects. This study's design also decreased its reliability; it used a 21-day prospective design in a before–after clinical trial and did not use blinding or a placebo control during treatment.

Table 1. Single compound.

Compound	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
Diethyl azelate	21 days prospective, before–after	17	Completed		Decreased obesity	↓ TC/HDL ratio, LDL/HDL ratio, noncholesterol HDL/HDL ratio	[8]

TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein. ↓, decrease.

It was impossible to determine the trend of studies regarding the antiobesity effects of single compounds because there was only one study in this category.

2.2. Foods

Twenty-six human studies examined using foods to treat obesity (**Table 2**).

Table 2. Foods.

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
Allium sativum (aged garlic extract)	Double-blind, randomized, placebo-	48	Completed	NCT01959646	Decreased obesity	↓ LDL	[9]

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
	controlled clinical trial						
Citrus bergamia (bergamot) and *Cynara cardunculus*	Double-blind placebo-controlled clinical trial	86	Completed	ISRCTN12833814	Decreased BW	↓ LDL-C, HDL-C, non-HDL-C, TC	[10]
Glycine max (L.) Merr (black soybean testa extract)	8-week planned, randomized, double-blind, placebo-controlled clinical trial	63	Completed	NCT02108691	Decreased obesity	↓ TG, LDL, non-HDL	[11]
Carum carvi L. (caraway aqueous extract)	Triple-blind, placebo-controlled clinical trial	60	Completed	NCT01833377	Decreased obesity, appetite		[12]
Ceratonia siliqua (carob) and *Undaria pinnatifida* (wakame) enriched snack	8-week, randomized, placebo-controlled clinical trial	32	Completed	NCT03420989	Decreased obesity	↓ TC, resistin levels, LDL-C	[13]
Cynara scolymus (artichoke) extract	Double-blind, placebo-controlled, randomized clinical trial	54			Decreased obesity, decreased BW and BMI	↑ HDL; ↓TC, TC/HDL, LDL, LDL/HDL, ApoB, ApoB/ApoA	[14]
Allium sativum (garlic extract)	Randomized double-blind placebo-controlled nutritional intervention clinical trial with two parallel arms	92		DRKS00010533	Decreased obesity	↓ LDL-C	[15]
Vitis vinifera L. (grape) seed extract	Randomized, double-blind, placebo-controlled clinical trial	40	Completed	IRCT2015073015968N3	Decreased obesity	↓ NPY	[16]

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
Lactobacillus plantarum fermented *Hordeum vulgare-Triticum aestivum* (barley-wheat) flour compound noodle	Single-blinded, controlled, parallel clinical trial	30	Completed	ChiCTR1800019614	Decreased obesity	↓ TG	[17]
Lippia citriodora (lemon beebrush) and *Hibiscus sabdariffa* (roselle)	8-week, randomized, double-blind, placebo-controlled clinical trial	54	Completed		Decreased obesity, appetite	↓ Leptin, resistin	[18]
Matured *Humulus lupulus* L. (hops)	Randomized, double-blind, placebo-controlled parallel-arm clinical trial	178	Completed	UMIN000014185	Decreased BF		[19]
Gnetum gnemon Linn (melinjo) seed	Prospective, randomized, parallel, double-blind, placebo-controlled clinical trial	42	Completed	UMIN000025643	Increased APN multimerization	↑ HMW/total APN ratio	[20]
Nigella sativa (black seed or jintan hitam) and *Trigonella foenum-graecum* (fenugreek) supplemented chapatis	12-week prospective, before–after clinical trial	40	Completed		Decreased obesity	↓ TC, non-↑ HDL-C, VLDL, TG, ↓ HbA1C, FPG	[21]
Allium cepa L. (onion) peel	Randomized, double-blind, placebo-controlled clinical trial	61			Decreased obesity	↑ PUFA n-6 ↓ PUFA n-3	[22]
Platycodon grandiflorus	Single-center, randomized, double-blind,	72	Completed		Decreased obesity	PGE571: ↓ leptin.	[23]

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
(balloon flower) ethanol extract	placebo-controlled clinical trial					PGE2855: ↓ L:A ratio	
Quercetin-rich *Allium cepa* L. (onion) powder	Randomized, double-blind, placebo-controlled, parallel-group clinical trial	54	Completed	UMIN000033410	Subjects with lower HDL-C: decreased VFA.		[24]
Salvia officinalis (common sage)	Randomized triple-blinded placebo-controlled clinical trial	60	Completed	IRCT201504146917N2	Decreased obesity		[25]
Garcinia cambogia (Malabar tamarind) and *Amorphophallus konjac* (konjac)	Prospective, nonrandomized controlled intervention clinical trial	214	Completed		Decreased weight	↓ Cholesterol, TG	[26]
Stevia rebaudiana (stevia)	Randomized, three-arm, single-blinded crossover clinical trial	30	Completed	NCT01115088	Decreased energy intake		[27]
Helianthus annuus (sunflower) seed extract	Randomized, placebo-controlled, double-blind, parallel-group clinical pilot study	46	Completed		Decreased obesity	↓ Cholesterol, long-lasting LDL	[28]
Citrullus lanatus (watermelon)	Randomized 2-arm design with a single 6-week intervention period	45	Completed	NCT04015544	Decreased obesity		[29]
Caulerpa racemosa (green algae)	Randomized, double-blind, placebo-controlled clinical trial	74	Completed	NCT05037591	Decreased obesity	↑ HDL, proliferator-activated receptor-γ coactivator α (PGC-	[30]

rol; TG, body fat; ted fatty

C. carvi L. (caraway) aqueous extract (CAE) decreased WC, waist-to-hip ratio (WHR), thigh circumference (THC), and mid-upper arm circumference [12]. Rondanelli et al. demonstrated that *C. scolymus* (artichoke) decreased visceral adipose tissue (VAT), fat mass (FM), and WC [14]. These results demonstrated that artichokes could potentially treat individuals with overweight and impaired fasting glucose. *V. vinifera* L. (grape) seed extract (GSE) decreased several anthropometric measurements, including BW, BMI, WC, hip circumference (HC), and WHR, demonstrating its potential to treat obesity [16]. The treatment group received GSE (300 mg/day) for 12 weeks, also lowering neuropeptide Y (NPY) levels compared to the placebo group. An *L. plantarum* fermented barley–wheat flour compound noodle (FBWN) decreased WC, fat rate, FM, and visceral fat (VF) and increased muscle mass and basal metabolic rate [17]. Boix-Castejón et al. reported that combining *L. citriodora* (lemon beebrush) and *H.*

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
[18]						1α); ↓ TC, TG	
Cyperus rotundus rhizome extract [19]	Randomized, double-blind, parallel-group, placebo-controlled pilot study	30	Completed	CTRI/2014/05/004633	Decreased waist circumference and BMI	↓ TC, TG, LDL, VLDL; ↑ HDL	[31]
Garcinia cambogia (Malabar tamarind) extract	Open-label clinical study	100	Completed [20]		Improved anthropometric and metabolic state	↓ LDL; ↑ HDL	[32]
Hydrangea serrata (Thunb.) Ser. leaf extract	Randomized, double-blind, placebo-controlled clinical trial [21]	98 [23]	Completed	KCT0005594	Decreased overweight	↓ LDL, TG	[33]
Citrus reticulata (immature poken) extract	Randomized, placebo-controlled clinical trial	20	Completed	CMUH103-REC2-040	Decreased weight and fat metabolism by suppressing [24] adipogenesis	↓ LDL, TG, TC	[34]

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d that *S. officinalis* (common sage) decreased BW, BMI, and WC [25]. Common sage extract at 330 mg/day for eight weeks positively affected lipid metabolism. Maia-Landim et al. reported that standardized *G. cambogia* (Malabar tamarind) extracts (52.4% hydroxycitric acid (HCA)) and *A. konjac* (konjac; 94.9% glucomannan) decreased plasma glucose, cholesterol, and TG levels; FM; VF; and BW and increased the basal metabolic rate [26]. However, polymorphisms in perilipin 4 (*PLIN4*; −11482G > A), FM and obesity-associated (*FTO*; rs9939609 (A/T)), and β-adrenergic receptor 3 (*ADRB3*; Trp64Arg) attenuated its lipolysis effect. Farhat et al. reported that *S. rebaudiana* (stevia) intake did not result in energy compensation during lunch or throughout the day and reduced postprandial glucose levels compared to sugar [27]. Stevia was found to lower appetite and stop the increase in food intake. Leverrier et al. reported that 500 mg/day of *H. annuus* (sunflower) seed extract for 12 weeks decreased cholesterol, long-lasting LDL, BW, BMI, and WC [28]. The intervention was especially effective in females with obesity aged >30 years.

Six weeks of *C. lanatus* (watermelon) supplementation increased fasting plasma L-arginine, cis-lycopene, and trans-lycopene levels and decreased vascular cell adhesion molecule 1 (VCAM1) levels [29]. This study only suggested indirect effects on obesity, so further research is needed to obtain effective results for lipid metabolism. A new comprehensive study by Permatasari et al. showed that *C. racemosa* (green seaweed or green algae) could be a new candidate for antiobesity functional food [30]. This study integrated in silico and in vitro experiments with a four-week, randomized, double-blind, placebo-controlled clinical trial. A randomized, double-blind, parallel-group, placebo-controlled pilot study by Majeed et al. demonstrated the antiobesity potential of *C. rotundus* extract (CRE) [31]. Interestingly, CRE showed antiadipogenic activity, was safe for human consumption, and effectively managed weight and hypercholesterolemia in individuals with overweight.

The main active ingredient in Malabar tamarind extract is HCA, which is known to attenuate weight gain and fat synthesis in animals and humans [32]. However, the mechanism underlying the action of HCA is not fully

understood. A three-month clinical study on 100 individuals with obesity and a subsequent computational study investigated the effect of HCA treatment on anthropometric measurements and plasma lipid profiles in human subjects [32]. They showed that HCA could reduce weight gain and fat accumulation in subjects with obesity. Han et al. conducted a randomized, double-blind, placebo-controlled study assessing the effect of standardized *H. serrata* (Thunb.) Ser. leaf extract (WHS) on BW and BF reduction in human subjects with overweight or obesity [33]. Daily WHS supplementation reduced BW, BMI, and BFM. Interestingly, this was accompanied by reduced HC, VFA, abdominal fat area, and the visceral–subcutaneous ratio. More interestingly, no significant side effects were observed during or after 12 weeks of this intervention.

All the above studies support the claim that certain foods help prevent obesity. Foods used in these studies were usually also treated as herbal medicines, and many processed foods into extracts to test their effects on obesity. Certain foods reduce obesity usually by controlling metabolic hormones or reducing appetite. Most studies stated that there were no side effects. However, some studies used noodle or snack forms to test the food's antiobesity effect [13][17]. Moreover, some studies did not clearly indicate a mechanism for reducing obesity. Therefore, further studies are needed.

2.3. Teas

Twelve human studies treated obesity using tea (**Table 3**). Yonekura et al. conducted a cross-sectional study on *C. arabica* (coffee) and *C. sinensis* (green tea). These substances were administered to 232 Japanese women aged 40–65 years with menopausal symptoms who completed the brief-type self-administered diet history questionnaire [35]. Patients were divided into four groups depending on their coffee (CF) and green tea (GT) consumption. Using a multivariate model, they showed an inverse relationship between daily CF/GT intake and BW, BMI, and cardio-ankle vascular index. Ghasemi et al. conducted a clinical trial using combined high-intensity interval training and green tea supplementation in 30 women with overweight [36]. They determined that daily green tea consumption increased the levels of sirtuin 1 (SIRT1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and catalase (CAT) and significantly decreased BFP, BMI, and BW. Therefore, the catechins in green tea inhibit lipogenesis, increase fat oxidation, and improve antioxidant capacity. Kobayashi et al. conducted a randomized, double-blind, placebo-controlled trial examining the effectiveness of green tea beverages enriched with catechins and a galloyl moiety on obesity in 124 subjects with obesity [37]. Green tea catechins with a galloyl moiety reduced BW, BMI, and BFP by decreasing abdominal fat area via inhibiting or attenuating intestinal fat absorption.

Table 3. Teas.

Tea	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
Coffea arabica (coffee), *Camellia sinensis* (green tea)	Cross-sectional, brief-type self-administered	232	Completed		Decreased BW and BMI		[35]

Tea	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
	diet history questionnaire						
Coffee, green tea	Cross-sectional, Japan multi-institutional collaborative cohort study	3539	Completed		Coffee: decreased VAT, metabolic syndrome		[38]
Decaffeinated green coffee bean extract	Randomized, double-blind, placebo-controlled trial	43	Completed	NCT02764957	Decreased obesity and appetite		[39]
Green coffee bean extract	Randomized, double-blind, placebo-controlled clinical trial	64	Completed		Decreased obesity	↑ Serum adiponectin; ↓ total serum cholesterol, LDL, FFA, leptin	[40]
Green tea	10-week randomized, placebo-controlled trial	30	Completed	NCT04950062	Increased metabolic status	↑ PGC-1α	[36]
Green tea	Randomized, double-blind, placebo-controlled clinical trial	124	Completed		Decreased BF		[37]
Green tea extract	Double-blinded placebo-controlled trial	45	Completed	IRCT20151025024699N3	Decreased obesity	↑ Adiponectin, irisin	[41]
High-dose green tea extract (epigallocatechin gallate)	Randomized, single-center, placebo-controlled, double-blind study	77	Unknown	NCT02147041	Decreased weight	↑ Adiponectin; ↓ cholesterol, LDL, ghrelin	[42]
Kosen-cha	12-week, prospective,	6	Completed		Decreased obesity	↓TG, ↑insulin	[43]

Tea	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
	before–after study					sensitivity	
Oolong tea	14-day, placebo-controlled, double-blind, crossover intervention trial	12	Completed		Increased FO		[44]
Puer tea extract	Randomized, double-blind, placebo-controlled clinical trial	59	Completed	NCT03613688	Decreased obesity	↓ Cholesterol	[45]

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Six studies demonstrated the effectiveness of fruit-derived natural products in ameliorating obesity (**Table 4**). Duchnowicz et al. reported that *A. melanocarpa* decreased acetylcholinesterase (AChE) activity and oxidative stress, improving lipid metabolism related to cholinesterase activity [46]. *A. melanocarpa* at 3 × 100 mg/day for two months decreased cholesterol and lipid peroxidation, reducing AChE. Rondanelli et al. found that bergamot phytosome positively affected VAT after 30 days and remained effective for a further 60 days [47]. Bergamot phytosome tablets (500 mg) taken twice daily for 12 weeks modulated lipids, decreasing TC and LDL and increasing HDL. All these studies support the efficacy of fruit-derived natural products against obesity and lipid disorders, although there were some limitations. Treatments in several studies appeared effective but were not significant. In addition, a few studies were conducted on obesity-related bioavailability, such as metabolic disorders, inflammatory status, and antioxidant capacity, rather than on obesity itself.

Table 4. Fruits.

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
Aronia melanocarpa extract	Placebo-controlled trial	77	Completed		Decreased cholinesterase activity	↑ HDL, cholesterol, TAC “fast” parameter; ↓ TC, LDL, TG, TAC “slow” parameter, lipid peroxidation, cholesterol in the erythrocyte membranes	[46]
Citrus bergamia (bergamot) phytosome	Randomized, double-blind, placebo-controlled trial	64	Completed		Decreased VAT	↓ TC, LDL, ApoB, LDL/HDL; ↑ ApoA/HDL	[47]

Extract	Study Design	Population	Status	Number	Outcome	Lab Test	Reference
Citrus bergamia (bergamot) polyphenol extract-complex	Randomized, double-blind, placebo-controlled trial	45	Completed	UNICZ Trial No. 182/2016	Decreased weight	↓ TC, LDL, TAG, serum leptin, serum ghrelin; ↑ HDL, serum adiponectin	[48]
Citrus bergamia (bergamot)	Randomized, double-blind, placebo-controlled trial	98	Completed		Decreased cholesterol and BW	↓ LDL	[49]
Grape pomace and *Schisandra chinensis* (omija) fruit ethanol extract	Randomized, double-blind, placebo-controlled trial	76	Completed		Decreased obesity-related dyslipidemia	High GO: ↑ ApoA-1; ↓ TC, non-HDL-C, LDL-C, plasma ApoB, Apo B/ApoA-1 ratio, plasma Lp(a)	[50]
Euterpe edulis (juçara) pulp powder	Randomized, double-blind trial	35	Completed	RBR-5RXR2B	Decreased obesity	↑ HDL-C, serum adiponectin; ↓ TC, LDL, TAG, L:A ratio	[51]
Garcinia mangostana (mangosteen) extract	26-week prospective randomized, controlled, parallel-group study	20	Completed	NCT02823561	Decreased weight	↓ HDL	[52]

HDL, high-density lipoprotein; TAC, total antioxidant capacity; TC, total cholesterol; LDL, low-density lipoprotein; TG, triacylglycerols; VAT, visceral adipose tissue; ApoB, apolipoprotein B; ApoA, apolipoprotein A; TAG, triacylglycerols; BW, body weight; ApoA-1, apolipoprotein A-1; Lp(a), lipoprotein(a); L:A ratio, leptin-to-adiponectin ratio; ↓, decrease; ↑, increase.

Obesity is a global burden with continuously high prevalence rates [53]. While current technologies and synthetic medicines are being adopted to treat obesity, their related complications and safety issues are still being discussed. Traditional herbal medicines have arisen as effective agents to alleviate this multifactorial disease, and various studies have scrutinized the antiobesity effects of natural products. While many

References

1. World Health Organization. Obesity. Available online: https://www.who.int/health-topics/obesity#tab=tab_1 (accessed on 22 November 2022).
2. Kim, K.-S.; Yang, H.J.; Choi, E.-K.; Shin, M.H.; Kim, K.-H.; Um, J.Y.; Lee, B.-C.; Jang, H.-J. The effects of complex herbal medicine composed of Cornus fructus, Dioscoreae rhizoma, Aurantii fructus, and Mori folium in obese type-2 diabetes mice model. Orient. Pharm. Exp. Med. 2013, 13, 69–75.
3. World Health Organization. World Obesity Day 2022—Accelerating Action to Stop Obesity. Available online: https://www.who.int/news/item/04-03-2022-world-obesity-day-2022-accelerating-action-to-stop-obesity (accessed on 22 November 2022).

4. Centers for Disease Control and Prevention. Health Effects of Overweight and Obesity. Available online: https://www.cdc.gov/healthyweight/effects/index.html (accessed on 22 November 2022).
5. National Institute of Diabetes and Digestive and Kidney Diseases. Prescription Medications to Treat Overweight & Obesity. Available online: https://www.niddk.nih.gov/health-information/weight-management/prescription-medications-treat-overweight-obesity (accessed on 22 November 2022).
6. Tak, Y.J.; Lee, S.Y. Long-Term Efficacy and Safety of Anti-Obesity Treatment: Where Do We Stand? Curr. Obes. Rep. 2021, 10, 14–30.
7. Lee, S.E.; Lim, C.; Lim, S.; Lee, B.; Cho, S. Effect of Ephedrae Herba methanol extract on high-fat diet-induced hyperlipidaemic mice. Pharm. Biol. 2019, 57, 676–683.
8. Streeper, R.T.; Louden, C.; Izbicka, E. Oral Azelaic Acid Ester Decreases Markers of Insulin Resistance in Overweight Human Male Subjects. In Vivo 2020, 34, 1173–1186.
9. Xu, C.; Mathews, A.E.; Rodrigues, C.; Eudy, B.J.; Rowe, C.A.; O'Donoughue, A.; Percival, S.S. Aged garlic extract supplementation modifies inflammation and immunity of adults with obesity: A randomized, double-blind, placebo-controlled clinical trial. Clin. Nutr. ESPEN 2018, 24, 148–155.
10. Perro, T.; Montalcini, T.; Mazza, E.; Foti, D.; Angotti, E.; Gliozzi, M.; Nucera, S.; Paone, S.; Bombardelli, E.; Aversa, T.; et al. Randomized Clinical Trial: Bergamot Citrus and Wild Cardoon Reduce Liver Steatosis and Body Weight in Non-diabetic Individuals Aged Over 50 Years. Front. Endocrinol. 2020, 11, 494.
11. Lee, M.; Sorn, S.R.; Park, Y.; Park, H.K. Anthocyanin Rich-Black Soybean Testa Improved Visceral Fat and Plasma Lipid Profiles in Overweight/Obese Korean Adults: A Randomized Controlled Trial. J. Med. Food 2016, 19, 995–1003.
12. Kazemipoor, M.; Hamzah, S.; Hajifaraji, M.; Radzi, C.W.; Cordell, G.A. Slimming and Appetite-Suppressing Effects of Caraway Aqueous Extract as a Natural Therapy in Physically Active Women. Phytother. Res. 2016, 30, 981–987.
13. Izaola, O.; Primo, D.; Rico Bargués, D.; Martín-Diana, A.B.; Martínez Villaluenga, C.; Miranda, J.; de Luis Román, D.A. Effects of a snack enriched with carob and Undaria pinnatifida (wakame) on metabolic parameters in a double blind, randomized clinical trial in obese patients. Nutr. Hosp. 2020, 34, 465–473.
14. Rondanelli, M.; Riva, A.; Petrangolini, G.; Allegrini, P.; Bernardinelli, L.; Fazia, T.; Peroni, G.; Gasparri, C.; Nichetti, M.; Faliva, M.A.; et al. The Metabolic Effects of Cynara Supplementation in Overweight and Obese Class I Subjects with Newly Detected Impaired Fasting Glycemia: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial. Nutrients 2020, 12, 3298.

3. Discussion

3.1. Antiobesity Mechanism

Based on the reviewed studies, natural products that demonstrated efficacy in alleviating obesity shared common mechanisms. Major mechanisms included lipid metabolism, anti-inflammation, antioxidation, appetite loss, and thermogenesis. The efficacy was evident in regulating lipid parameters, cytokines, hormones, or genes. By comprehensively understanding the efficacy and related mechanisms, this research extensively identified the potential effects of various natural products for treating obesity.

3.1.1. Lipid Metabolism

Various studies identified lipid metabolism when discussing how the target compound works to treat obesity (**Figure 1** and **Figure 2**). Forty-five studies were regarded to have a lipid metabolism pathway, although nine studies lacked an appropriate mechanism.

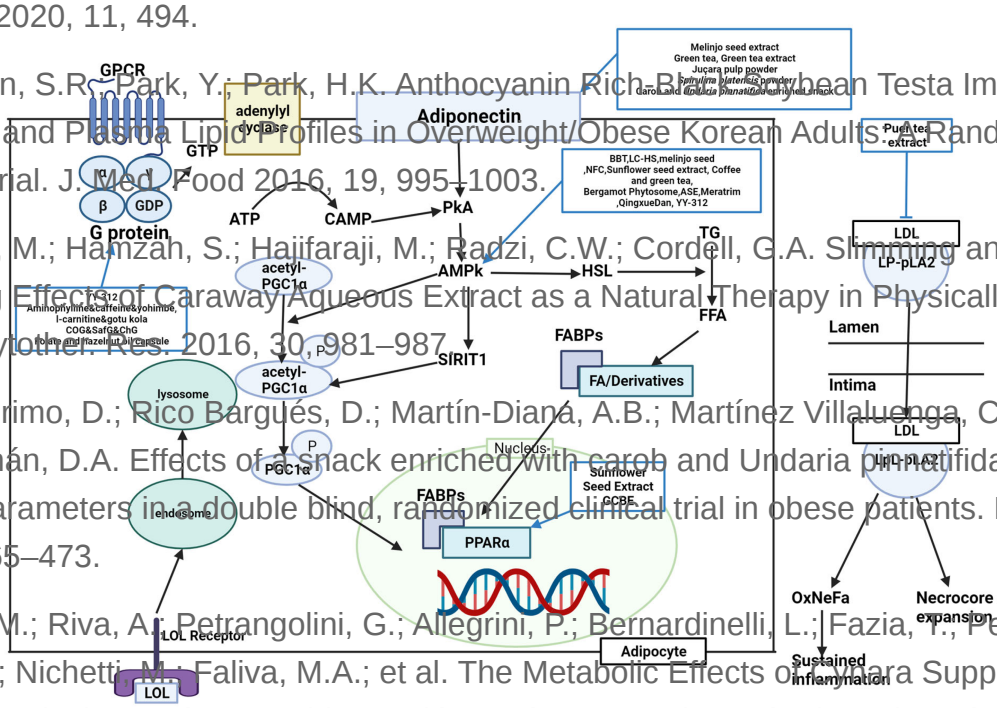

Figure 1. Schematic diagram of lipid metabolism and the effects of natural products. BB4, black soybean testa extract; LPL, lipoproteinlipase; HSL, hormone sensitive lipase; AMPK, adenosine monophosphate-activated

protein kinase; NFC, *Nigella sativa* and *Trigonella foenum graecum* supplement capsules; LC-HS, *Lippia citriodora* L. and *Hibiscus sabdariffa* L.; ASE, *Aster spathulifolius* Maxim extract; OPE, onion peel extract; CPT-1α, carnitine palmitoyltransferase 1 alpha; GCBE, green coffee bean extract; YY-312, *Imperata cylindrica* Beauvois, *Citrus unshiu* Markovich, and *Evodia officinalis* Dode; PPARα, peroxisome proliferator-activated receptor alpha; Lp-PLA2, lipoprotein-associated phospholipase A2; LDL, low-density lipoprotein; CoG, coconut oil group; SafG, safflower oil group; ChG, chia oil Group; GTP, guanosine triphosphate; ADRB3, A/T-, and β-adrenergic receptor 3; GPCR, G protein-coupled receptor; GTP, guanosine triphosphate; ATP, adenosine triphosphate; cAMP, cyclic adenosine monophosphate; AMPK, adenosine monophosphate-activated protein kinase; TG, triglycerides; FFA, free fatty acids; FABPs, fatty acid-binding protein; FA, fatty acid; OxNeFa, oxidized nonesterified fatty acids; PGC1α, peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; PKA, protein kinase A; LpL-PLA2, lysophospholipid-associated phospholipase A2.

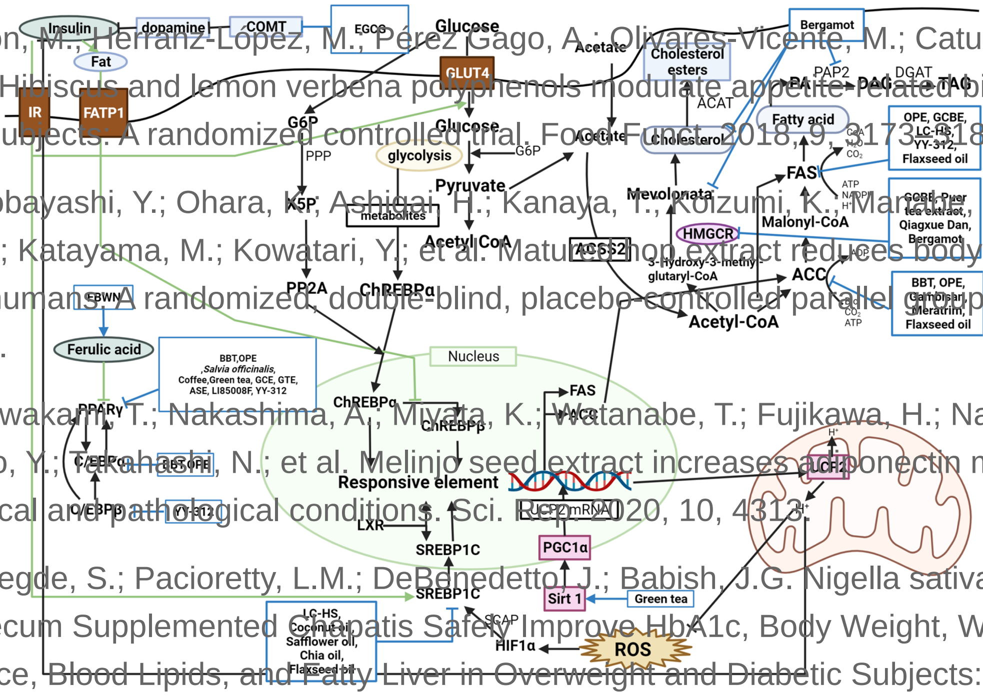

Figure 2. Schematic diagram of glucose metabolism and the effects of natural products. PPARγ, peroxisome proliferator-activated receptor gamma; BBT, black soybean testa extract; OPE, onion peel extract; GCBE, green coffee bean extract; GTE, green tea extract; ASE, *Aster spathulifolius* Maxim extract; LI85008F, *Moringa oleifera* leaf aqueous ethanol extract, *Murraya koenigii* (L.) Spreng. leaf aqueous ethanol extract, and *Curcuma longa* L. extract; YY-312, *Imperata cylindrica* Beauvois, *Citrus unshiu* Markovich, and *Evodia officinalis* Dode; ACC, acetyl-CoA carboxylase; ATP, adenosine triphosphate; ADP, adenosine diphosphate; C/EBPα, CCAAT-enhancer-binding protein alpha; FAS, fatty acid synthase; PA, phosphatidic acid; PAP2, type-2 phosphatidic acid phosphatase; DAG, diacylglycerol; DGAT, diacylglycerol-acyltransferase; TAG, triacylglycerol; LC-HS, *Lippia citriodora* L. and *Hibiscus sabdariffa* L.; NADPH, nicotinamide adenine dinucleotide phosphate; CoA, coenzyme A; C/EBPβ, CCAAT/enhancer-binding protein beta; HMGCR, HMG-CoA reductase; ACAT, acylCoA cholesterol acyl transferase; srebp-1c, sterol regulatory element-binding protein 1c; LXR, liver X receptor; FBWN, *Lactobacillus plantarum* fermented barley-wheat flour compound noodle; COMT, catechol-O-methyltransferase; IR, insulin receptor; FATP1,

15. Szulińska, M.; Kręgielska-Narożna, M.; Świątek, J.; Styś, P.; Kuźnar-Kamińska, B.; Jakubowski, H.; Walkowiak, J.; Bogdański, P. Garlic extract favorably modifies markers of endothelial function in obese patients—Randomized double blind placebo-controlled nutritional intervention. Biomed. Pharmacother. 2018, 102, 792–797.
16. Parandoosh, M.; Yousefi, R.; Khorsandi, H.; Nikpayam, O.; Saidpour, A.; Babaei, H. The effects of grape seed extract (Vitis vinifera) supplement on inflammatory markers, neuropeptide Y, anthropometric measures, and appetite in obese or overweight individuals: A randomized clinical trial. Phytother. Res. 2020, 34, 379–387.
17. Pan, R.; Xu, T.; Bai, J.; Xia, S.; Liu, Q.; Li, J.; Xiao, X.; Dong, Y. Effect of Lactobacillus plantarum fermented barley on plasma glycolipids and insulin sensitivity in subjects with metabolic syndrome. J. Food Biochem. 2020, 44, e13471.
18. Boix-Castejón, M.; Herranz-López, M.; Pérez Gago, A.; Olivares-Vicente, M.; Caturla, N.; Roche, E.; Micol, V. Hibiscus and lemon verbena polyphenols modulate appetite-related biomarkers in overweight subjects: A randomized controlled trial. Food Funct. 2018, 9, 3173–3184.
19. Morimoto-Kobayashi, Y.; Ohara, K.; Ashigai, H.; Kanaya, T.; Koizumi, K.; Manabe, F.; Kaneko, Y.; Taniguchi, Y.; Katayama, M.; Kowatari, Y.; et al. Matured hop extract reduces body fat in healthy overweight humans: A randomized, double-blind, placebo-controlled parallel group study. Nutr. J. 2016, 15, 25.
20. Oniki, K.; Kawakami, T.; Nakashima, A.; Miyata, K.; Watanabe, T.; Fujikawa, H.; Nakashima, R.; Nasu, A.; Eto, Y.; Takahashi, N.; et al. Melinjo seed extract increases adiponectin multimerization in physiological and pathological conditions. Sci. Rep. 2020, 10, 4313.
21. Rao, A.S.; Hegde, S.; Pacioretty, L.M.; DeBenedetto, J.; Babish, J.G. Nigella sativa and Trigonella foenum-graecum Supplemented Chapatis Safely Improve HbA1c, Body Weight, Waist Circumference, Blood Lipids, and Fatty Liver in Overweight and Diabetic Subjects: A Twelve-Week Safety and Efficacy Study. J. Med. Food 2020, 23, 905–919.
22. Choi, H.N.; Choue, R.; Park, Y.; Yim, J.E. Onion Peel Extract Increases Erythrocyte Membrane n-3 Fatty Acids in Overweight and Obese Korean Subjects. J. Med. Food 2020, 23, 37–42.
23. Kim, Y.J.; Kwon, E.Y.; Kim, J.W.; Lee, Y.; Ryu, R.; Yun, J.; Kim, M.; Choi, M.S. Intervention Study on the Efficacy and Safety of Platycodon grandiflorus Ethanol Extract in Overweight or Moderately Obese Adults: A Single-Center, Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients 2019, 11, 2445.
24. Nishimura, M.; Muro, T.; Kobori, M.; Nishihira, J. Effect of Daily Ingestion of Quercetin-Rich Onion Powder for 12 Weeks on Visceral Fat: A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study. Nutrients 2019, 12, 91.

fatty acid transport protein 1; GLUT4, glucose transporter type 4; G6P, glucose-6-phosphate; Acetyl CoA, acetyl coenzyme A; ACSS2, acetyl-CoA synthetase 2; ChREBP, carbohydrate response element binding protein α; ChREBPβ, carbohydrate response element binding protein β; UCP2, uncoupling protein 2; ROS, reactive oxygen species; HIF-1α, hypoxia-inducible factor 1; SCAP, stem cells from apical papilla; SIRT1, sirtuin-1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; UCP2 mRNA, uncoupling protein 2 messenger RNA; PPP, phosphatidate phosphohydrolase; X5P, xylulose 5-phosphate; PP2A, protein phosphatase 2A.

Lipid metabolism is classified into lipogenesis, lipolysis, and adipocyte differentiation, and the corroborated antiobesity effects are explained by suppressing lipogenesis, accumulation, and adipocyte differentiation and inducing lipolysis and fatty acid oxidation. Peroxisome proliferator-activated receptor gamma (PPARγ), acetyl-CoA carboxylase (ACC), CCAAT-enhancer-binding protein alpha (C/EBPα), CCAAT/enhancer-binding protein beta (C/EBPβ), fatty acid synthase (FAS), and sterol regulatory element-binding protein 1c (SREBP-1C) are lipogenic factors. Lipoprotein lipase (LPL), hormone-sensitive lipase (HSL), peroxisome proliferator-activated receptor alpha (PPARα), and adenosine monophosphate (AMP)-activated protein kinase (AMPK) are lipolysis factors. Several studies found these factors to regulate obesity complexly.

PPARγ was downregulated by BBT, OPE, common sage, coffee, green tea, GCBE, GTE, ASE, LI85008F, and YY-312 [11][22][25][35][39][41][54][55][56]. BBT, OPE, Gambisan, Meratrim, and flaxseed oil are associated with ACC inhibition [11][22][57][58][59]. BBT and OPE have been reported to downregulate C/EBPα [11][22]. FAS was inhibited by OPE, GCBE, LC-HS, YY-312, and flaxseed oil [22][40][55][59][60]. YY-312 downregulated C/EBPβ, thereby inhibiting adipocyte differentiation [55]. BBT upregulated lipolysis proteins such as LPL and HSL [11]. AMPK is predominantly associated with antiobesity metabolism. BBT, LC-HS, melinjo seed, NFC, sunflower seed extract, coffee and green tea, bergamot phytosome, ASE, LC-HS, Meratrim, Qingxue Dan, and YY-312 were reported to activate AMPK [11][18][20][21][28][35][47][54][55][57][60][61]. OPE upregulated carnitine palmitoyltransferase I alpha (CPT-1α) [22]. Sunflower seed extract and GCBE upregulated *PPARα* expression [28][40]. APN was upregulated by a carob- and wakame-enriched snack, melinjo seed, green tea, GTE, juçara pulp powder, and *S. platensis* powder, decreasing lipogenesis and inducing β-oxidation [13][20][36][41][51][62]. Pancreatic lipase was inhibited by PTE, mangosteen extract, Gambisan, and Qingxue Dan [45][52][58][61]. HMG-CoA reductase (HMGCR), a cholesterol synthesis enzyme, was inhibited by GCBE, PTE, and Qingxue Dan [40][45][61]. PTE acts as a noncompetitive inhibitor of lipoprotein-associated phospholipase A2 (Lp-PLA2) [45]. LC-HS, coconut oil, safflower oil, chia oil, and flaxseed oil suppressed SREBP-1C [59][60][63]. A carob- and wakame-enriched snack and Qingxue Dan activated the LDL receptor, inhibiting lipid synthesis [13][61]. YY-312, Lipoxyderm, coconut oil, safflower oil, chia oil, and folate and hazelnut oil capsules altered steps in the process in which activation of guanosine triphosphate (GTP)-binding proteins successively activates adenylate cyclase, cyclic AMP (cAMP), and protein kinase A (PKA), and lipase [55][63][64][65]. GCBE and bergamot inhibited the activation of acyl-CoA cholesterol acyltransferase (ACAT) [40][49]. GCBE upregulated carnitine palmitoyltransferase, a fatty acid oxidation enzyme [40]. FBWN increased ferulic acid, inhibiting lipid accumulation and regulating lipid metabolism [17]. High-dose GTE increased fat oxidation by inhibiting catechol-O-methyltransferase (COMT) [42]. Quercetin-rich onion powder altered the expression of genes related to fat metabolism, such as ADRB3, HSL, PPARγ, and uncoupling protein (UCP)-2 [24]. Standardized

25. Amini, L.; Mojab, F.; Jahanfar, S.; Sepidarkish, M.; Raoofi, Z.; Maleki-Hajiagha, A. Efficacy of Salvia officinalis extract on the prevention of insulin resistance in euglycemic patients with polycystic ovary syndrome: A double-blinded placebo-controlled clinical trial. Complement. Ther. Med. 2020, 48, 102245.
26. Maia-Landim, A.; Ramírez, J.M.; Lancho, C.; Poblador, M.S.; Lancho, J.L. Long-term effects of Garcinia cambogia/Glucomannan on weight loss in people with obesity, PLIN4, FTO and Trp64Arg polymorphisms. BMC Complement. Altern. Med. 2018, 18, 26.
27. Farhat, G.; Berset, V.; Moore, L. Effects of Stevia Extract on Postprandial Glucose Response, Satiety and Energy Intake: A Three-Arm Crossover Trial. Nutrients 2019, 11, 3036.
28. Leverrier, A.; Daguet, D.; Calame, W.; Dhoye, P.; Kodimule, S.P. Helianthus annuus Seed Extract Affects Weight and Body Composition of Healthy Obese Adults during 12 Weeks of Consumption: A Randomized, Double-Blind, Placebo-Controlled Pilot Study. Nutrients 2019, 11, 1080.
29. Shanely, R.A.; Zwetsloot, J.J.; Jurrissen, T.J.; Hannan, L.C.; Zwetsloot, K.A.; Needle, A.R.; Bishop, A.E.; Wu, G.; Perkins-Veazie, P. Daily watermelon consumption decreases plasma sVCAM-1 levels in overweight and obese postmenopausal women. Nutr. Res. 2020, 76, 9–19.
30. Permatasari, H.K.; Nurkolis, F.; Hardinsyah, H.; Taslim, N.A.; Sabrina, N.; Ibrahim, F.M.; Visnu, J.; Kumalawati, D.A.; Febriana, S.A.; Sudargo, T.; et al. Metabolomic Assay, Computational Screening, and Pharmacological Evaluation of Caulerpa racemosa as an Anti-obesity With Anti-aging by Altering Lipid Profile and Peroxisome Proliferator-Activated Receptor-γ Coactivator 1-α Levels. Front. Nutr. 2022, 9, 1412.
31. Majeed, M.; Nagabhushanam, K.; Bhat, B.; Ansari, M.; Pandey, A.; Bani, S.; Mundkur, L. The Anti-Obesity Potential of Cyperus rotundus Extract Containing Piceatannol, Scirpusin A and Scirpusin B from Rhizomes: Preclinical and Clinical Evaluations. Diabetes, Metab. Syndr. Obes. 2022, 15, 369–382.
32. Tomar, M.; Rao, R.P.; Dorairaj, P.; Koshta, A.; Suresh, S.; Rafiq, M.; Kumawat, R.; Paramesh, R.; Bu, V.; Venkatesh, K.V. A clinical and computational study on anti-obesity effects of hydroxycitric acid. RSC Adv. 2019, 9, 18578–18588, Erratum in RSC Adv. 2019, 9, 22288.
33. Han, H.-S.; Chung, K.-S.; Shin, Y.-K.; Yu, J.-S.; Kang, S.-H.; Lee, S.-H.; Lee, K.-T. Effect of Standardized Hydrangea serrata (Thunb.) Ser. Leaves Extract on Body Weight and Body Fat Reduction in Overweight or Obese Humans: A Randomized Double-Blind Placebo-Controlled Study. Nutrients 2022, 14, 208.
34. Lin, Y.K.; Chung, Y.M.; Yang, H.T.; Lin, Y.H.; Lin, Y.H.; Hu, W.C.; Chiang, C.F. The potential of immature poken (Citrus reticulata) extract in the weight management, lipid and glucose metabolism. J. Complement. Integr. Med. 2021, 19, 279–285.

extracts of Malabar tamarind, konjac regulated lipolysis by activating cAMP signaling [26]. Green tea increased SIRT1-mediated PGC-1α activity, decreasing adipocyte differentiation, proliferation, and the expression of genes involved in lipogenesis [36]. Melinjo seed inhibited HMG-CoA and reduced cholesterol levels, mevalonate levels, and hepatic TG accumulation by inhibiting phosphatidate phosphohydrolase activity [49].

3.1.2. Anti-Inflammation

Twenty-one natural products modulated the inflammation pathway, and twenty studies explained their mechanisms (**Figure 3**).

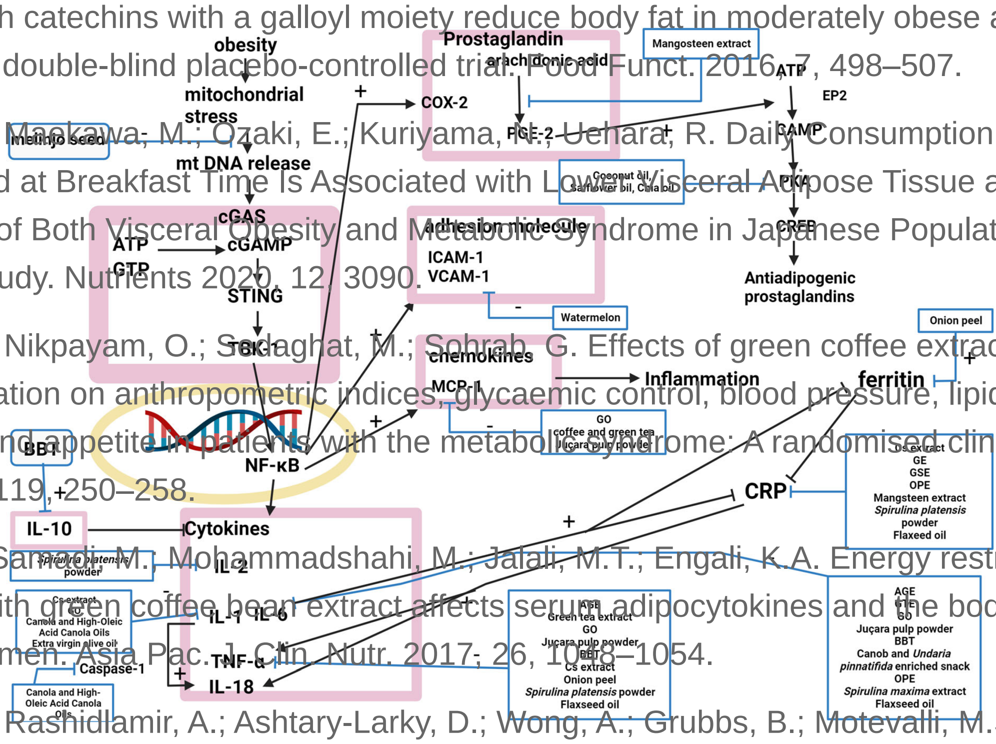

Figure 3. The nuclear factor-kappa B (NF-κB) signaling pathway was inhibited by AGE, GTE, GO, and juçara pulp powder, attenuating the production of proinflammatory cytokines and suppressing obesity-induced inflammation [9][41][50][51]. NF-κB inhibition decreases the circulating levels of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin (IL)-6. IL-6 was decreased by AGE, BBT, ascarob- and wakame-enriched snack, OPE, GTE, GO, juçara pulp powder, *S. maxima* extract, and flaxseed oil [9][11][13][22][41][50][51][59][66]. TNF-α was inhibited by AGE, BBT, artichoke extract, GSE, onion peel, GTE, GO, juçara pulp powder, *S. platensis* powder, and flaxseed oil [9][11][14][16][22][41][50][51][59][62]. Coffee and green tea, GO, and juçara pulp powder downregulated the expression of monocyte chemoattractant protein-1 (MCP-1), inhibiting monocyte adhesion [35][50][51]. Artichoke extract, GE, GSE, OPE, mangosteen extract, *S. platensis*powder, and flaxseed oil decreased high-sensitivity C-reactive protein (hsCRP) levels [14][15][16][22][52][59][62]. GO, canola oil, high-oleic-acid canola oil, and extra virgin olive oil reduced IL-1β [50][67][68]. BBT increased IL-10 [11]. Artichoke extract regulated IL-1 and interferon (IFN) [14]. Melinjo seed activated the cGMP-AMP (cGAMP) synthase-cGAMP-stimulator of interferon genes pathway by activating disulfide bond A oxidoreductase-like protein (DSBA-L) [20]. Onion peel decreased ferritin [22]. Watermelon decreased VCAM-1, intercellular adhesion molecule 1 (ICAM-1), and P-selectin, which attracts immune cells to

35. Yonekura, Y.; Terauchi, M.; Hirose, A.; Odai, T.; Kato, K.; Miyasaka, N. Daily Coffee and Green Tea Consumption Is Inversely Associated with Body Mass Index, Body Fat Percentage, and Cardio-Ankle Vascular Index in Middle-Aged Japanese Women: A Cross-Sectional Study. Nutrients 2020, 12, 1370.

36. Ghasemi, E.; Afzalpour, M.E.; Nayebifar, S. Combined high-intensity interval training and green tea supplementation enhance metabolic and antioxidant status in response to acute exercise in overweight women. J. Physiol. Sci. 2020, 70, 31.

37. Kobayashi, M.; Kawano, T.; Ukawa, Y.; Sagesaka, Y.M.; Fukuhara, I. Green tea beverages enriched with catechins with a galloyl moiety reduce body fat in moderately obese adults: A randomized double-blind placebo-controlled trial. Food Funct. 2016, 7, 498–507.

38. Koyama, T.; Maekawa, M.; Ozaki, E.; Kuriyama, N.; Uehara, R. Daily Consumption of Coffee and Eating Bread at Breakfast Time Is Associated with Lower Visceral Adipose Tissue and with Lower Prevalence of Both Visceral Obesity and Metabolic Syndrome in Japanese Populations: A Cross-Sectional Study. Nutrients 2020, 12, 3090.

39. Roshan, H.; Nikpayam, O.; Sedaghat, M.; Sohrab, G. Effects of green coffee extract supplementation on anthropometric indices, glycaemic control, blood pressure, lipid profile, insulin resistance and appetite in patients with the metabolic syndrome: A randomised clinical trial. Br. J. Nutr. 2018, 119, 250–258.

40. Haidari, F.; Samadi, M.; Mohammadshahi, M.; Jalali, M.T.; Engali, K.A. Energy restriction combined with green coffee bean extract affects serum adipocytokines and the body composition in obese women. Asia Pac. J. Clin. Nutr. 2017, 26, 1048–1054.

41. Bagheri, R.; Rashidlamir, A.; Ashtary-Larky, D.; Wong, A.; Grubbs, B.; Motevalli, M.S.; Baker, J.S.; Laher, I.; Zouhal, H. Effects of green tea extract supplementation and endurance training on irisin, pro-inflammatory cytokines, and adiponectin concentrations in overweight middle-aged men. Eur. J. Appl. Physiol. 2020, 120, 915–923.

42. Chen, I.J.; Liu, C.Y.; Chiu, J.P.; Hsu, C.H. Therapeutic effect of high-dose green tea extract on weight reduction: A randomized, double-blind, placebo-controlled clinical trial. Clin. Nutr. 2016, 35, 592–599.

43. Katanasaka, Y.; Miyazaki, Y.; Sunagawa, Y.; Funamoto, M.; Shimizu, K.; Shimizu, S.; Sari, N.; Shimizu, Y.; Wada, H.; Hasegawa, K.; et al. Kosen-cha, a Polymerized Catechin-Rich Green Tea, as a Potential Functional Beverage for the Reduction of Body Weight and Cardiovascular Risk Factors: A Pilot Study in Obese Patients. Biol. Pharm. Bull. 2020, 43, 675–681.

44. Zhang, S.; Takano, J.; Murayama, N.; Tominaga, M.; Abe, T.; Park, I.; Seol, J.; Ishihara, A.; Tanaka, Y.; Yajima, K.; et al. Subacute Ingestion of Caffeine and Oolong Tea Increases Fat Oxidation without Affecting Energy Expenditure and Sleep Architecture: A Randomized, Placebo-Controlled, Double-Blinded Cross-Over Trial. Nutrients 2020, 12, 3671.

damaged areas of the mouth, lumen [29]. Mangosteen extract inhibited the conversion of arachidonic acid to prostaglandin E2 (PGE2) by down-regulating cyclooxygenase (COX) and COX-2 gene expression [52]. IL-2 was decreased by *S. platensis* supplementation [62]. [illegible] inhibited the [illegible] inflammasome-mediated caspase-1 (CASP1) activity [68]. Coconut, safflower, and chia oils upregulated cAMP-dependent signaling pathways, which produce antiadipogenic prostaglandins that function in the adaptive reactions of cyclooxygenases [63].

3.1.3. Antioxidant

The next mechanism associated with antiobesity is antioxidation (**Figure 4**). Ten studies noted antioxidant effects, but only two discussed the antioxidant mechanism associated with their compound's significant efficacy.

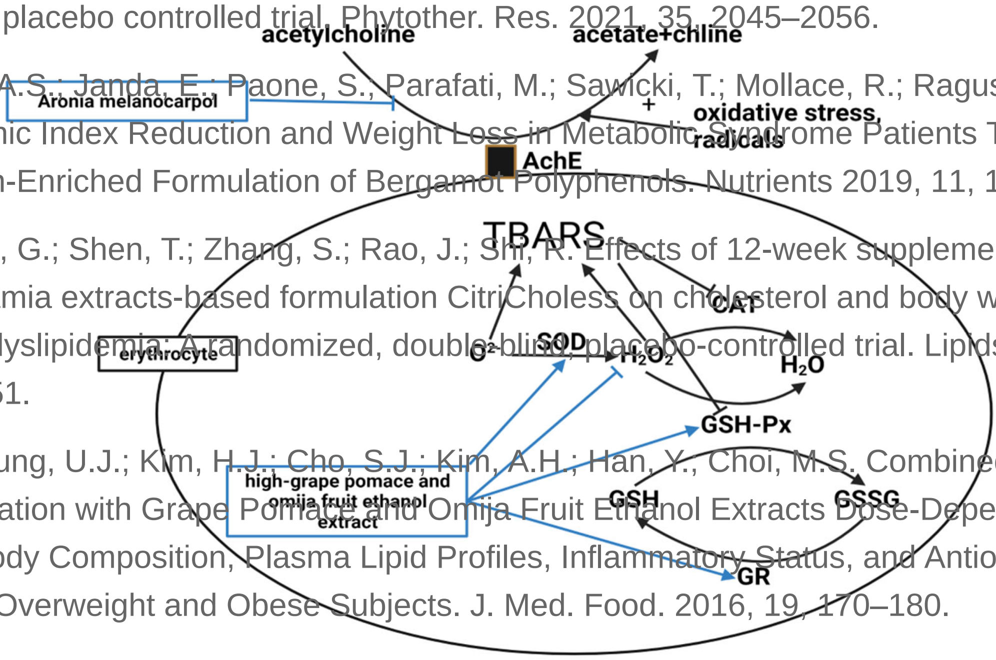

Figure 4. High oxidative stress and free radicals increase AChE activity. However, *A. melanocarpa* decreased the AChE activity in the erythrocyte membranes [46]. Superoxide dismutase (SOD) catalyzes the dismutation of the superoxide anion to H_2O_2, then catalase (CAT) and glutathione peroxidase (GSH-Px) degrade H_2O_2. GSH-Px also oxidizes reduced glutathione (GSH) to oxidized glutathione (GSSG), and GSSG is reduced to GSH by glutathione reductase (GR). A high-GO supplement elevated erythrocyte SOD, GSH-Px, and GR activities and lowered H_2O_2 levels [50]. Thiobarbituric acid reactive substances (TBARS), a marker of lipid peroxidation caused by oxidative injury, were also reduced by the high-GO supplement [50].

3.1.4. Appetite Loss

Twelve studies established a connection between appetite and the effects of natural products, and nine mentioned the mechanism underlying this effect (**Figure 5**). Among the three excluded studies, one did not show a significant appetite suppression effect but reported a related mechanism. Appetite loss manifests as increased anorexigenic factors and decreased orexigenic factors.

45. Jensen, G.S.; Beaman, J.L.; He, Y.; Guo, Z.; Sun, H. Reduction of body fat and improved lipid profile associated with daily consumption of a Puer tea extract in a hyperlipidemic population: A randomized placebo-controlled trial. Clin. Interv. Aging 2016, 11, 367–376.

46. Duchnowicz, P.; Ziobro, A.; Rapacka, E.; Koter-Michalak, M.; Bukowska, B. Changes in Cholinesterase Activity in Blood of Adolescent with Metabolic Syndrome after Supplementation with Extract from Aronia melanocarpa. Biomed. Res. Int. 2018, 2018, 5670145.

47. Rondanelli, M.; Peroni, G.; Riva, A.; Petrangolini, G.; Allegrini, P.; Fazia, T.; Bernardinelli, L.; Naso, M.; Faliva, M.A.; Tartara, A.; et al. Bergamot phytosome improved visceral fat and plasma lipid profiles in overweight and obese class I subject with mild hypercholesterolemia: A randomized placebo controlled trial. Phytother. Res. 2021, 35, 2045–2056.

48. Capomolla, A.S.; Janda, E.; Paone, S.; Parafati, M.; Sawicki, T.; Mollace, R.; Ragusa, S.; Mollace, V. Atherogenic Index Reduction and Weight Loss in Metabolic Syndrome Patients Treated with A Novel Pectin-Enriched Formulation of Bergamot Polyphenols. Nutrients 2019, 11, 1271.

49. Cai, Y.; Xing, G.; Shen, T.; Zhang, S.; Rao, J.; Shi, R. Effects of 12-week supplementation of Citrus bergamia extracts-based formulation CitriCholess on cholesterol and body weight in older adults with dyslipidemia: A randomized, double-blind, placebo-controlled trial. Lipids Health Dis. 2017, 16, 251.

50. Han, H.J.; Jung, U.J.; Kim, H.J.; Cho, S.J.; Kim, A.H.; Han, Y.; Choi, M.S. Combined Supplementation with Grape Pomace and Omija Fruit Ethanol Extracts Dose-Dependently Improves Body Composition, Plasma Lipid Profiles, Inflammatory Status, and Antioxidant Capacity in Overweight and Obese Subjects. J. Med. Food. 2016, 19, 170–180.

51. Jamar, G.; Santamarina, A.B.; Flygare, A.C.; Gagliardi, A.; de Rosso, V.V.; Dourado, V.Z.; Pisani, L.P. Effects of the juçara fruit supplementation on metabolic parameters in individuals with obesity: A double-blind randomized controlled trial. J. Nutr. Biochem. 2020, 83, 108430.

52. Watanabe, M.; Gangitano, E.; Francomano, D.; Addessi, E.; Toscano, R.; Costantini, D.; Tuccinardi, D.; Mariani, S.; Basciani, S.; Spera, G.; et al. Mangosteen Extract Shows a Potent Insulin Sensitizing Effect in Obese Female Patients: A Prospective Randomized Controlled Pilot Study. Nutrients 2018, 10, 586.

53. Chooi, Y.C.; Ding, C.; Magkos, F. The epidemiology of obesity. Metab. Clin. Exp. 2019, 92, 6–10.

54. Cho, I.J.; Choung, S.Y.; Hwang, Y.C.; Ahn, K.J.; Chung, H.Y.; Jeong, I.K. Aster spathulifolius Maxim extract reduces body weight and fat mass in obese humans. Nutr. Res. 2016, 36, 671–678.

55. Cho, Y.G.; Jung, J.H.; Kang, J.H.; Kwon, J.S.; Yu, S.P.; Baik, T.G. Effect of a herbal extract powder (YY-312) from Imperata cylindrica Beauvois, Citrus unshiu Markovich, and Evodia

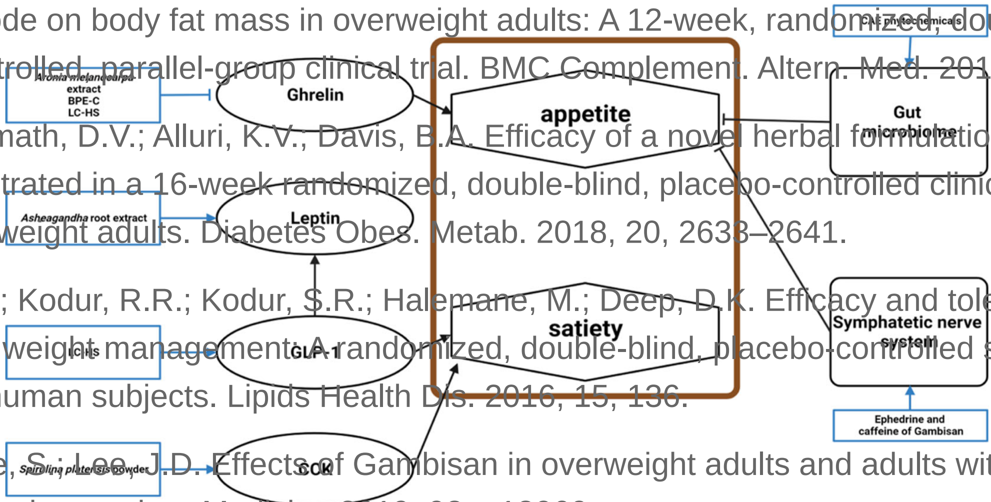

Figure 5. Schematic diagram of the appetite mechanism in obesity and the effects of natural products. BPE-C, bergamot polyphenol extract complex; LC-HS, *Lippia citriodora* and *Hibiscus sabdariffa*; GLP-1, glucagon-like peptide-1; CCK, cholecystokinin; CAE, caraway aqueous extract.

Ghrelin was lowered by *A. melanocarpa* extract, BPE-C, and LC-HS [46][48][60]. LC-HS increased glucagon-like peptide-1 (GLP-1), an anorexigenic incretin produced by the intestinal L-cells that stimulates insulin secretion and induces satiety [18][60]. Ashwagandha root extract reduced stress, restoring leptin levels, which suppresses food intake [69]. CAE phytochemicals, including limonene, γ-terpinene, trans-carveol, carvone, thymol, and carvacrol, improved the gastrointestinal microbiome to alter appetite [12]. The phycocyanin component of *S. platensis* powder may be responsible for cholecystokinin release, which affects the brain's appetite center [62]. The ephedrine and caffeine in Gambisan reversed obesity by reducing food intake via the sympathetic nervous system [58].

3.1.5. Thermogenesis

Ten studies mentioned the relationship between thermogenesis and the effects of natural products, though one only stated the effects without explaining the mechanism (**Figure 6**). Increased thermogenic gene expression and factors caused the browning of white adipose tissues.

officinalis Dode on body fat mass in overweight adults: A 12-week, randomized, double-blind, placebo-controlled, parallel-group clinical trial. BMC Complement. Altern. Med. 2017, 17, 375.

56. Dixit, K.; Kamath, D.V.; Alluri, K.V.; Davis, B.A. Efficacy of a novel herbal formulation for weight loss demonstrated in a 16-week randomized, double-blind, placebo-controlled clinical trial with healthy overweight adults. Diabetes Obes. Metab. 2018, 20, 2633–2641.

57. Kudiganti, V.; Kodur, R.R.; Kodur, S.R.; Halemane, M.; Deep, D.K. Efficacy and tolerability of Meratrim for weight management: A randomized, double-blind, placebo-controlled study in healthy overweight human subjects. Lipids Health Dis. 2016, 15, 136.

58. Jo, D.H.; Lee, S.; Lee, J.D. Effects of Gambisan in overweight adults and adults with obesity: A retrospective chart review. Medicine 2019, 98, e18060.

59. Rezaei, S.; Sasani, M.R.; Akhlaghi, M.; Kohanmoo, A. Flaxseed oil in the context of a weight loss programme ameliorates fatty liver grade in patients with non-alcoholic fatty liver disease: A randomised double-blind controlled trial. Br. J. Nutr. 2020, 123, 994–1002.

60. Herranz-López, M.; Olivares-Vicente, M.; Boix-Castejón, M.; Caturla, N.; Roche, E.; Micol, V. Differential effects of a combination of Hibiscus sabdariffa and Lippia citriodora polyphenols in overweight/obese subjects: A randomized controlled trial. Sci. Rep. 2019, 9, 2999.

61. Chung, W.; Ryu, J.; Chung, S.; Kim, S. Effect of Qingxue Dan on obesity and metabolic biomarker: A double-blind randomized-controlled pilot study. J. Tradit. Chin. Med. 2016, 36, 291–298.

62. Yousefi, R.; Mottaghi, A.; Saidpour, A. Spirulina platensis effectively ameliorates anthropometric measurements and obesity-related metabolic disorders in obese or overweight healthy individuals: A randomized controlled trial. Complement. Ther. Med. 2018, 40, 106–112.

63. Oliveira-de-Lira, L.; Santos, E.M.C.; de Souza, R.F.; Matos, R.J.B.; Silva, M.C.D.; Oliveira, L.D.S.; Nascimento, T.G.D.; Schemly, P.; Souza, S.L. Supplementation-Dependent Effects of Vegetable Oils with Varying Fatty Acid Compositions on Anthropometric and Biochemical Parameters in Obese Women. Nutrients 2018, 10, 932.

64. Escalante, G.; Bryan, P.; Rodriguez, J. Effects of a topical lotion containing aminophylline, caffeine, yohimbe, l-carnitine, and gotu kola on thigh circumference, skinfold thickness, and fat mass in sedentary females. J. Cosmet. Dermatol. 2019, 18, 1037–1043.

65. Lima, R.P.A.; do Nascimento, R.A.F.; Luna, R.C.P.; Persuhn, D.C.; da Silva, A.S.; da Conceição Rodrigues Gonçalves, M.; de Almeida, A.T.C.; de Moraes, R.M.; Junior, E.V.; Fouilloux-Meugnier, E.; et al. Effect of a diet containing folate and hazelnut oil capsule on the methylation level of the ADRB3 gene, lipid profile and oxidative stress in overweight or obese women. Clin. Epigenetics 2017, 9, 110.

66. Szulinska, M.; Gibas-Dorna, M.; Miller-Kasprzak, E.; Suliburska, J.; Miczke, A.; Walczak-Gałezewska, M.; Stelmach-Mardas, M.; Walkowiak, J.; Bogdanski, P. Spirulina maxima improves insulin sensitivity, lipid profile, and total antioxidant status in obese patients with well-treated hypertension: A randomized double-blind placebo-controlled study. Eur. Rev. Med. Pharmacol. Sci. 2017, 21, 2473–2481.
67. Galvão Cândido, F.; Xavier Valente, F.; da Silva, L.E.; Gonçalves Leão Coelho, O.; Gouveia Peluzio, M.D.C.; Gonçalves Alfenas, R.C. Consumption of extra virgin olive oil improves body composition and blood pressure in women with excess body fat: A randomized, double-blinded, placebo-controlled clinical trial. Eur. J. Nutr. 2018, 57, 2445–2455.
68. Liu, X.; Kris-Etherton, P.M.; West, S.G.; Lamarche, B.; Jenkins, D.J.; Fleming, J.A.; McCrea, C.E.; Pu, S.; Couture, P.; Connelly, P.W.; et al. Effects of canola and high-oleic-acid canola oils on abdominal fat mass in individuals with central obesity. Obesity 2016, 24, 2261–2268.
69. Choudhary, D.; Bhattacharyya, S.; Joshi, K. Body Weight Management in Adults Under Chronic Stress Through Treatment With Ashwagandha Root Extract: A Double-Blind, Randomized, Placebo-Controlled Trial. J. Evid. Based Complement. Altern. Med. 2017, 22, 96–106.

Figure 6. Schematic diagram of the thermogenesis mechanism in obesity and the effects of natural products. ASE, *Aster spathulifolius* Maxim extract; OPE, onion peel extract; PGE, *Platycodon grandiflorus* ethanol extract; GCBE, green coffee bean extract; UCP-1, uncoupling protein-1; UCP-2, uncoupling protein-2; ADRB3, adrenoceptor beta-3; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PPARα, peroxisome proliferator-activated receptor alpha; SIRT1, sirtuin 1; ↑, increase.

A carob- and wakame-enriched snack, melinjo seed, OPE, PGE, and GCBE induced uncoupling protein-1 (*UCP1*) in brown adipose [13][20][22][23][40]. ASE increased uncoupling protein-2 (*UCP2*) expression, increasing energy expenditure and consumption [54]. The sympathetic nervous system was considered related to energy expenditure through thermogenesis. Matured hop and Gambisan were believed to activate the nerve system [19][58]. PGE increased the expression of thermogenic-related genes, such as *SIRT1*, *PPARα*, and *PGC-1α* [23]. Folate and hazelnut oil capsules lowered *ADRB3* gene methylation levels [65]. The ADRB3 protein facilitates the catecholamine-induced activation of adenylate cyclase through the actions of G proteins. These mechanisms are involved in energy homeostasis by mediating thermogenesis.

It is evident that various studies have examined the effects of natural products on obesity. This research detailed the potential for the widespread use of natural products in treating obesity, which has not been reported in previous reviews on the same topic. Further studies on safety, tolerability, and pharmacokinetics can be performed on these natural products to confirm their potential effectiveness. Natural compounds, foods, tea, fruit, extracts, decoctions, and external preparations were found to show efficacy in lipid metabolism, anti-inflammation, antioxidation, appetite loss, and thermogenesis. Most studies showed positive effects in relieving the symptoms of obesity and demonstrated that natural products could be used as effective treatments for obesity. Therefore, herbal medicines are expected to be fully utilized in clinical obesity treatment. However, limitations remain in that some studies did

not investigate efficacy or safety, and their nonsignificant results could be changed with precise control of drug dosages. Therefore, meta-analyses are needed to further examine their findings. Further studies are expected to refine the pharmacological effects of natural products for clinical use.