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Malaysian Herbaceous and Shrub Species with Anti-Obesity Properties: A Review

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Abstract: Obesity is a widespread public health problem worldwide and is associated with numerous health risks, requiring effective prevention and treatment strategies. Although synthetic anti-obesity drugs are available, they often cause adverse side effects, thus generating interest in natural products as safer and more effective alternatives. Malaysian shrub plants thrive in the country's tropical climate and offer a rich source of biological active compounds with potential anti-obesity effects. Several studies, including *in vivo* and clinical trials, have reported promising anti-obesity effects of these plants. Research on local plants not only aligns with public health priorities but also provides affordable interventions for the local population. This review systematically summarizes findings from 193 articles across electronic databases using relevant keywords, covering Malaysian herbaceous and shrub species with anti-obesity potential, their isolated compounds, proposed mechanisms of action, and supporting *in vitro*, animal model, and clinical evidence. In addition, toxicological data are discussed to provide a comprehensive perspective of the therapeutic potential of these plants. This review highlights the gaps in current knowledge and proposes future directions for leveraging Malaysian plants to combat obesity.

Keywords: Obesity; anti-obesity; herbaceous plants; shrubs.

1. Introduction

Obesity is a chronic disease characterized by excess body fat. It is defined by the International Classification of Diseases (ICD-11) [1]. Body mass index (BMI) is the standard tool for diagnosing obesity and calculated in kilograms of body weight per square metre [2]. According to the World Health Organization (WHO), a normal BMI for adults is 19.8 to 26.0, overweight is 26.0 to 29.9, and obesity is above 30.0 [2]. For children, BMI is adjusted for age and gender [3]. In 2022, WHO reported that 2.5 billion adults were overweight and more than 890 million were classified as obese [2]. These findings are associated with major non-communicable diseases (NCDs), such as cardiovascular disease, type-2 diabetes, hypertension, and cancers like breast and kidney cancer [4,5].

Obesity has multiple causes, including genetic predisposition, unhealthy diets, sedentary lifestyles, and environmental factors [6,7]. The main causes are physical inactivity and overeating, where calorie intake exceeds energy expenditure, leading to fat storage [8,9]. In fact, energy consumption depends on basal metabolism, the thermogenic effect of digestion and physical activity [10]. In addition, a high-calorie, carbohydrate-rich diets elevate blood sugar levels, triggering insulin release and fat accumulation [11]. Genetic factors, such as leptin deficiency, can also disrupt appetite regulation [8]. Furthermore, diseases such as polycystic ovarian syndrome and hypothyroidism, as well as certain medications, can lead to weight gain [12]. Emotional factors, such as stress and boredom, further influence overeating habits [13].

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Treating obesity is costly and challenging. While synthetic drugs, such as orlistat, liraglutide, and phentermine-topiramate, are available in treating obesity [14]. These drugs are expensive and often cause adverse side effects, such as cardiovascular issues, nausea, and liver damage [14]. Therefore, natural products are emerging as safer and more affordable alternatives for obesity management. These plant-based remedies offer promising potential to improve public health, reduce healthcare costs, and provide sustainable solutions to obesity [15].

Natural products and their structural analogues have made significant contributions to many pharmacotherapies throughout history. Natural products are now preferred over synthetic drugs because they are effective in treating overweight and various chronic conditions and can reduce the side effects of synthetic drugs [16]. Traditional herbal remedies that have been widely used throughout history, along with other natural ingredients, have shown good promise in reducing appetite and promoting weight loss [17]. Generally, natural materials are perceived as more affordable and have fewer or no toxic side effects than synthetic ingredients [16,17]. Natural products differ from their pharmaceutical products in that they are often complex mixtures in which the identity and quantity of the bioactive components present are not fully known. Therefore, the isolation of bioactive chemical components from natural sources is an important step in natural product research. In addition, the isolated bioactive molecules can be used as chemical markers to assess the quality and safety of natural products and to determine their efficacy [18].

Malaysia is a home to a diverse range of plant species, many of which may offer natural solutions to obesity [19]. Malaysia's year-round summers, tropical climate and flourishing ecosystems make many medicinal plants available throughout the year, providing optimal conditions for the continuous growth of numerous medicinal plants. In fact, many of the plants have been used historically for weight control and to promote health. In the modern era, research efforts have been increasingly focused on exploring the bioactive compounds in these plants that can be developed into modern products for the use in the fight against obesity. Herbaceous plants and shrubs are sustainable and accessible sources of bioactive compounds due to their small size, rapid growth, and widespread availability. This review focuses specifically on these plant types to highlight their potential as cost-effective and scalable solutions to combat obesity, particularly in regions such as Malaysia, where the abundance and historical uses of these plants present promising opportunities for modern therapeutic applications.

2. Methodology

Well-established databases, such as SciFinder, Scopus, Web of Science, ScienceDirect, Google Scholar and ResearchGate, were used in this review. The literature search employed the following keywords to obtain relevant literature, including 'anti-obesity', 'weight loss', and 'Malaysian shrubs'. A total of 845 articles were initially downloaded. However, after careful screening, only 193 articles were considered relevant to the scope of this review.

3. Mechanisms of Action of Anti-obesity Natural Compounds

3.1. Appetite Suppression

Increasing satiety is a way to suppress appetite and thus reduce food intake to control body weight, as hunger is always associated with excessive energy intake. The biological mechanism of appetite and satiety are controlled by a complex interaction of neural and hormonal signals. Potential mechanisms for suppressing appetite include increasing noradrenaline levels, which activates the sympathetic nervous system. This activation leads to increased satiety, increased energy expenditure, decreased hunger and enhanced fat oxidation. For example, the hormone leptin produced by adipose tissues, activates receptors in the central nervous system to reduce appetite and increase energy expenditure. In addition, insulin sends signals to the brain to maintain energy balance and reduce appetite. Leptin and insulin signals synergistically to suppress the urge to eat [20]. Moreover, some studies have shown that neuropeptides (such as serotonin, histamine, and dopamine) and their respective receptor activity play a role in regulating satiety. Targeting these neuropeptides and

receptors may be a promising approach to developing supplements designed to reduce energy intake and treat obesity by enhancing satiety [21]. Therefore, further research should explore natural substances that can alter brain signals involved in regulating appetite, thereby potentially providing new avenues for treating obesity.

3.2. Increase in Energy Expenditure

An imbalance between energy intake and energy expenditure is the primary cause of body fat accumulation [11]. Energy intake refers to the calories consumed through diet, while energy expenditure refers to the calories burned through physical activity and metabolic processes. When energy intake exceeds energy expenditure, the excess energy is stored in adipose tissue in the form of triglycerides (TG). To lose weight, energy expenditure must be greater than energy intake, resulting in a negative energy balance. This can be achieved by increasing physical activity through regular exercise and adaptive thermogenesis.

Adaptive thermogenesis refers to changes in energy expenditure that occur in respond to environmental conditions, dietary changes, or hormonal variations. It includes processes such as heat production through brown fat (non-shivering thermogenesis) or muscle contraction (shivering thermogenesis), in response to cold (cold-induced thermogenesis) or after eating (diet-induced thermogenesis) [22]. This mechanism helps regulate body weight by influencing how much energy the body expends in different situations. For example, in non-shivering thermogenesis, brown adipose tissue plays a key role in converting energy from food into heat. Thermogenic proteins are essential for this thermogenic function within brown adipose tissue. Therefore, a substance that can increase energy expenditure by enhancing the expression of thermogenic genes may have an anti-obesity effect [23]

3.3. Inhibition of Pancreatic Lipase (PL)

Pancreatic lipase (PL) is the most important enzyme in the digestive process because it directly affects the absorption of fatty acids in the intestine. It is the major lipase secreted by the pancreas and is present in visceral and subcutaneous adipocytes. Its function is to break down dietary fat (triglycerides) into fatty acids and glycerol, thereby facilitating fat absorption in the human intestine [24]. One possible approach to treating obesity is to disrupt the absorption of fat in the gastrointestinal tract. Natural products that can inhibit pancreatic lipase activity have been extensively studies as an important indicator for evaluating their potential to treat obesity and promote weight loss [25]. An example of a PL inhibitor is Orlistat, which has a half-maximal inhibitory concentration (IC_{50}) of 0.7 μM and is one of the FDA-approved weight loss drugs that has been reported to reduce dietary fat absorption by up to 30% [1]. However, Orlistat has several unacceptable side effects [14]. Therefore, there is a need to discover new and effective pancreatic lipase inhibitors from natural products.

3.4. Inhibition of Adipocyte Differentiation

Adipocytes are essential for regulating lipid balance and energy homeostasis. They have a remarkable ability to store triglycerides and to release free fatty acids in response to varying energy demands. As adipose tissue grows, adipocytes increase in both number (hyperplasia) and size (hypertrophy). This has prompted the exploration of natural products in anti-obesity treatments focused on inhibiting adipogenesis. In addition, some studies have shown that blocking certain transcription factors may hamper adipocyte differentiation [26].

3.5. Regulation of Lipid Metabolism

Enhanced lipolysis increases hydrolysis of triglyceride, thereby reducing fat storage in adipose tissue and helping to control obesity. Therefore, improving lipolysis is one of the potential approaches to treat obesity. Many studies have revealed some methods to enhance lipolysis. For example, activation of adenosine monophosphate-activated protein kinase (AMPK) enhances fatty acid oxidation and glucose transport in skeletal muscle. In addition, activation of β-adrenergic receptors in white adipocytes promotes lipolysis and non-shivering thermogenesis in brown fat. Therefore, transcription factors that mimic these effects are becoming increasingly important in the development of anti-obesity treatments [16].

4. Malaysian Plants Studied that Show Anti-obesity Activity

Growing concerns about the impact of obesity on global health have prompted scientists and researchers to focus more on discovering new, effective, and safe anti-obesity drugs, especially those from natural sources. The biological advantages of these natural products mainly come from their rich phytochemicals [27]. Although the anti-obesity properties of many plants have been investigated through ethnobotanical and ethnopharmacological studies [28], information on their chemical entities remains scarce. The potential of natural products to combat obesity remains largely undiscovered and represents a promising alternative for the development of safe and effective weight loss therapies. Ethnopharmacological studies have shown that many plants that have been traditionally used in different cultures for weight control have potential anti-obesity effects. These plants contain bioactive compounds that affects metabolic processes, reduce fat absorption, promote thermogenesis and suppress appetite. Plant extract plays an important role in anti-obesity analysis as it determines the potential of the plant as anti-obesity candidate. In this review, researchers in previous studies first analysed plant extracts followed by isolated compounds from their respective potential extracts. Most of the analyses performed by researchers were lipase inhibition assay, especially pancreatic lipase and adipocyte differentiation inhibition. Table 1 summarizes the anti-obesity properties of different herbaceous and shrubs plant species studied in Malaysia, either crude extracts or purified single compounds.

4.1. Alpinia officinarum

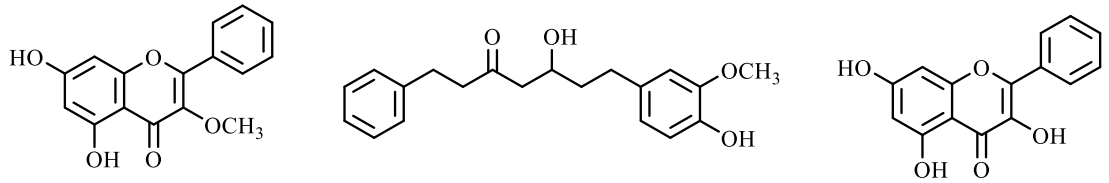
Alpinia officinalis belongs to the Zingiberaceae family and is a perennial herb commonly used in traditional Chinese medicine [29]. It is widely distributed in China, Indonesia, Thailand, and Malaysia, and is also cultivated in Bangladesh and southern India. It has a wide range of therapeutic effects, such as treating colds, coughs, respiratory tract and digestive system diseases, female infertility, rheumatism, antitussive, influenza, malaria, stomach pain, diabetes, and epilepsy [29].

A study by Shin et al. [30] showed that the ethyl acetate extract of the rhizome of *A. officinalis* exhibited the highest PL inhibitory activity in vitro. In their study, 3-methylethergalangin (**1**) (Figure 1) was isolated and found to have PL inhibitory activity with an IC_{50} value of 1.3 mg/mL, while Orlistat was used as a positive control (IC_{50} value = 0.8 mg/mL). In their *in vivo* experiment, serum triglyceride levels in corn oil-fed mice (induced hypertriglyceridemia) were significantly reduced compared with the control group after administration of the ethyl acetate fraction at dose of 500 mg/kg. In addition, a reduction of serum triglyceride (TG) and cholesterol levels were observed in Triton WR-1339-induced hyperlipidemic mice. When 3-methylethergalangin was administrated at dose of 20 mg/kg, triglyceride and cholesterol levels in Triton WR-1339-induced hyperlipidemic mice were significantly reduced by 81.3% and 81.0%, respectively. It also increased high-density lipoprotein (HDL) levels compared with the control group [30]. However, the extract (500 mg/kg, p.o.) and isolated compound (20 mg/kg, p.o) were used only at extremely high doses. Although we assume that the extract and the isolated compound will have the same effects in humans and mice, the result obtained are therapeutically irrelevant in any case. For a meaningful pharmacological study, the upper limit of the *in vivo* study dose range should be assumed to be 100 – 200 mg/kg for the extract, and 200

µg/kg for the pure compound, respectively [31]. In addition, both the studies used high single-dose experiments (500 mg/kg, p.o. for the extract and 20 mg/kg for the isolated compound) which led to an obvious issue in their data reproducibility.

In a subsequent study by the same authors [32], another compound, 5-5-hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-1-phenyl-3-heptanone (**2**) (Figure 1), was isolated and found to have an inhibitory effect on pancreatic lipase with an IC_{50} value of 1.5 mg/mL. Serum triglyceride levels were significantly reduced in corn oil-fed mice, while serum triglyceride and cholesterol levels were reduced in Triton WR-1339-induced hyperlipidemic mice. However, no lipid-lowering activity was observed in hyperlipidemic mice induced by a high cholesterol diet. Regarding pancreatic lipase inhibition, both compounds showed good efficacy compared to the positive control (Orlistat) across parameters such as triglyceride, cholesterol, and high-density lipoprotein (HDL) levels. Nevertheless, Orlistat remained the most effective overall [32].

Jung et al. [33] investigated the anti-obesity effect of *A. officinarum* ethanol extract and galangin (**3**) from the extract on lipid accumulation in 3T3-L1 cells and their effects on obesity in mice fed a high-fat diet. The ethanol extract significantly inhibited 3T3-L1 adipocyte differentiation in a dose-dependent experiment. The ethanol extract suppressed the levels of C/EBPa, SREBP-1, and PPAR-c, which promote adipogenesis. Galangin (**3**) (Figure 1) suppressed the accumulation of triglyceride during cell differentiation. Galangin (**3**) significantly inhibited the protein levels of some adipogenic genes such as FAS, C/EBPa, CD36, and PPAR-c in a dose dependent manner. *In vivo* study was further conducted to confirm the anti-obesity effect of ethanol extract [33]. After administration of the ethanol extract, the body weight of mice fed a high-fat diet was significantly reduced compared with the group receiving only a high-fat diet under similar daily food intake conditions. In addition, the epididymal and perirenal fat pad weights of the high-fat diet-fed mice group supplemented with the ethanol extract were reduced, and the levels of liver lipids, insulin, leptin, triglycerides, and total cholesterol were also reduced. These results indicate that the ethanol extract is effective in reducing liver fat accumulation in obese mice, demonstrating the anti-obesity effects of the *A. officinarum* ethanol extract [33]. To date, no adverse side effects have been reported in toxicity studies [34,35]. Further studies on optimum dose and molecular mechanisms of action of the extract or its compounds should be focused on.



1 **2** **3**

Figure 1. Anti-obesity compounds isolated from *A. officinarum*

Table 1. Malaysian herbaceous and shrub plant species that show anti-obesity activity.

Name of plants (common name)	Plants parts	Isolated anti-obesity compounds	Proposed mechanism of action	*In vitro* studies	*In vivo* studies animal	*In vivo* studies human	Toxicity	Ref.
Herbaceous Plants								
Alpinia officinarum Hance (Galangal)	Rhizomes	3-Methylethergalangin **1** 5-Hydroxy-7-(4'-hydroxy-3'-methoxyphenyl)-1-phenyl-3-heptanone **2** Galangin **3**	Pancreatic lipase inhibition, reduce cholesterol, plasma triglyceride, hepatic leptin and lipid levels	Compound **1** and **2** showed PL inhibitory, IC_{50} = 1.3 and 1.5 mg/mL, respectively. 4.2% (w/w) of compound **3** in 70% EtOH extract showed antiadipogenic effect in 3T3-L1 cells.	0.5% (g/kg dietary weight) of 70% EtOH extract reduced body weight, fat mass, serum insulin, leptin, hepatic lipid, TG and total cholesterol levels in mice dose dependently.	No	None observed	[30, 32-35]
Arachis hypogaea (Peanut)	Nuts, shells	Luteolin **4**	Pancreatic lipase inhibition (peanut shell), lipolysis of 3T3-L1 adipocytes (peanut shell), increases satiety, energy efficiency and expenditure, dietary compensation	Compound **4** showed PL inhibitory, IC_{50} = 7.1 µM. 95% EtOH shell extract showed highest PL inhibition of 92% at 10 mg/mL dose dependently. The extract also reduced glycerol release from 3T3-L1 adipocytes.	1% (dietary weight) of 95% EtOH shell extract reduced weight gain and increased fecal lipid excretion in rats.	Lower body mass index, little or no weight change and lower LDL cholesterol in people who eat nuts for 8 weeks, 1-6 months and 2 weeks, respectively.	None observed in peanut shell and not reported for peanuts	[37-42]
Cosmos caudatus (Ulam raja, kenikir, cosmos, daoruangpharma)	Leaves	No	Pancreatic lipase inhibition	EtOH extract showed PL inhibition of 21.7 ± 1.3% at 1000 ppm.	100% EtOH extract at a dose level of 175 or 350 mg/kg reduced body weight gain, visceral fat mass, TG and leptin levels, but increased fecal fat excretion in rats.	No	Acute hepatotoxicity effects at high dose	[99-104]
Curcuma longa (Turmeric)	Rhizomes	Curcumin **13** Demethoxycurcumin **14** Bisdemethoxycurcumin **15**	Inhibits adipokine-induced angiogenesis and 3T3-L1 differentiation,	Compound **13** attenuated lipolysis at 10-20 µM; inhibits FAS with IC50 value of 26.8	Compound **13** suppressed body weight gain, serum, total cholesterol	No	Gastrointestinal upsets at high dose	[105-114]

			increases oxidation and fatty acid esterification, down regulates the expression of key transcription factors, inhibits MAPK, inhibits FAS, activates PPARg, increases glycerol release	µM; nearly completely suppress adipocyte differentiation and lipid accumulation at 20 µM dose dependently. EA fraction from MeOH extract reduced lipid accumulation by 46.6% and reduced intracellular TG level by 37.9% at 20 µg/mL.	concentration in mice at a dose level of 500 mg/kg; reduced lipid levels in white adipose tissue of obese mice at 0.1% (w/w dietary weight). Curcuminoids (73.4% of compound **13**, 16.1% of compound **14** and 10.5% of compound **15**) reduced epididymal adipose tissue weight, TG and cholesterol concentration dose dependently.			
Phaseolus vulgaris (Bean)	Beans	Phytohemagglutinin (PHA) Phaseolamin	Inhibits α-amylase, 3T3-L1 adipocytes differentiation, phytohemoagglutinin-mediated (lectin) release of cholecystokinin and glucagon-like peptides, appetite suppression, suppressed the mRNA expression level and the protein expression level of PPARγ, C/EBPα, SREBP1c, LPL and fatty acid binding protein.	70% (w/v) EtOH extract inhibit 3T3-L1 adipocytes differentiation by reducing lipid content in the mature adipocytes to 79.29% at 150 µg/mL and 35.13% at 300 µg/mL.	PHA at a dose level above 0.32g/kg reduced body dry weight of the rats. Aqueous extract from bean seeds reduced body weight gain of obese rats.	Aqueous extract reduced body weight, BMI and fat mass in males and females; Extract reduced body weight, BMI, waist circumference, adipose tissue thickness and fat mass in overweight men and women.	Toxic in high dose	[143 - 153]
Taraxacum officinale (Dandelion)	Roots, Leaves	No	Reduces adipogenesis and TG level in 3T3L1 adipocytes, pancreatic lipase	60% EtOH leaf and root extract reduced intracellular lipid droplet accumulation at	400 mg/kg of 95% EtOH extract decreased incremental plasma triglyceride	No	Unknown	[172 - 178]

			inhibition	the highest concentration of 600 µg/mL by ~20% compared with control cells, reduced cellular TG content by ~65% in cells treated with the leaf extract, and ~20% in cells treated with root extract. 95% EtOH leaf extract showed PL inhibitory, IC_{50} = 78.2 µg/mL.	levels in ICR mice at 90 and 180 min.			
Shrubs Plants								
Camellia sinensis	Leaves	(-)-Epigallocatechin-3 gallate **5** (-)-Epicatechin-3-gallate **6** Caffeine	Stimulates sympathetic nervous system, increases thermogenesis and fat oxidation, inhibit gastric and pancreatic lipase, suppresses leptin, increases triacylglycerol excretion, suppresses adipocyte differentiation, increases expression of genes involved in fatty acid synthesis and oxidation, decreases lipoprotein lipase, hormone-sensitive lipase, decrease UCP2, activation of AMPK, increases adiponectin and ghrelin level, modulation of intestinal microbiota	Compound **5** and **6** exhibited PL inhibitory, IC_{50} = 0.16, 0.14 µg/mL, respectively. Oolong tea water extract exhibited PL inhibitory, IC_{50} = 0.97 µg/mL. Compound **5** inhibited lipid accumulation and induced apoptosis of maturing 3T3-L1 preadipocytes dose dependently.	20 g/kg of water extract of green tea reduced fat gain and body fat in rats. 2% and 4% green tea powder reduced body weight gain, fat accumulation, food intake, total cholesterol and TG in female ICR mice. 5% oolong tea powder reduced the body weight gain and accumulation of liver TG in mice. 1000 mg/kg of water extract of aged oolong tea reduced body weight, TG, total cholesterol, HDL and LDL in mice. 1 or 3% purple leaf tea reduced food intake, lipid accumulation, fat deposition in the fatty	Reduced body weight, waist size and subcutaneous fat content in obese men and women who consume 8 g of oolong tea water extract a day for 6 weeks. Reduced body weight and increased energy expenditure in obese Thai who consumed 250 mg green tea extract according to requested dose for 12 weeks. Reduction in LDL and TG in obese women who consume	Hepatotoxicity	[43-64]

					tissue of mice. 0.25% (w/w) green tea reduced body weight gain in obese mice.	400 mg of green tea extract three times daily for 12 weeks. Reduction in weight, BMI and waist circumference in obese women who consumed 856.8 mg/day of compound **5** for 12 weeks.		
Capsicum annuum (Red pepper, hot pepper, paprika)	Fruits, seeds, flowers	9-Oxooctadeca-10,12-dienoic acids **7** Capsaicin **8** Capsiate **9** Dihydrocapsiate **10**	Improving satiety, thermogenesis, fat oxidation, increased energy expenditure, inhibition of adipocyte differentiation, prevention of adipogenesis, inhibition of lipoprotein lipase and pancreatic lipase, activation of AMPK, stimulation of lipolysis in adipose tissue and modulation of adipokine secretion from adipose tissue	Fraction 5-6-1 and fraction 6-6-1 from green pepper water extract decreased lipoprotein lipase mRNA expression level by 26.6% and 29.7%, respectively in 3T3-L1 cells. 70% EtOH flower extract inhibited PL inhibitory, IC50 = 3.54 ± 0.18 mg/mL. Compound **7** inhibited ACC with IC_{50} = 1.4 x 10^{-6} M. 100 µM of compound **8** inhibit adipocyte differentiation in 3T3-L1 cells via AMPK activation. MeOH extract increased glycerol release from adipocytes dose dependently. 50 and 250 µg/mL of compound **8** increased glycerol release from adipocytes. MeOH hot pepper seed	0.014% of compound **8** decreased visceral fat mass by 29% in rodents. Compound **8**-chitosan microsphere reduced body weight of obese rats at 3382 mg/kg/day for 5 weeks. 10 mg/kg of compound **9** increased oxygen consumption, carbohydrate and fat oxidation, while decreased body weight, abdominal fat accumulation, epididymal and perirenal fat weights.	Reduced energy intake in people who consumed CH-19 sweet pepper and a combination of compound **8** and green tea. Compound **8** suppressed hunger and increased satiety in patients. Compound **8** or compound (**9** and **10)** increased energy expenditure by 245 kJ/day, 58.56 kcal/day respectively meanwhile decreased the respiratory quotient by 0.216.	Possible hepatic effects	[65-85]

				extract reduced lipid accumulation in 3T3-L1 adipocyte.				
Cassia mimosoides L. var. *nomame* Makino	Leaves, fruits, aerial parts	Proanthocyanidin Flavan dimers (2S)-3',4',7'-Trihydroxyflavan-(48)-catechin **11**	Pancreatic lipase inhibition, decreases triacylglycerol levels, suppress adipogenesis and lipogenesis via AMPK pathway, downregulating the expression levels of CCAAT/enhancer-binding protein-alpha, PPARγ, SREBP1c, FAS and upregulating the acetyl-CoA carboxylase.	30% EtOH leaf extract reduced lipid accumulation of differentiated 3T3-L1 cells at 6.25 to 25 µg/mL. Aqueous EtOH aerial part extract which contain primarily proanthocyanidin exhibited PL inhibitory, IC_{50} = 0.1 to 0.071 mg/mL. Compound 11 exhibited PL inhibitory, IC_{50} = 5.5 mM.	100 mg/kg and 300 mg/kg of 30% EtOH leaf extract reduced body weight gain and body fat accumulation in mice dose dependently. 2.5% (dietary weight) of aqueous EtOH aerial part extract which contain primarily proanthocyanidin reduced body weight gain and fat content of the rats dose dependently.	No	None observed	[88-90]
Coleus forskohlii	Roots	Forskolin **12**	Activates cAMP, promotes breakdown of stored fat, increases basal metabolic rate, reduces food intake	Compound **12** activated cAMP by increasing glycerol release at 50µM.	50 g/kg of extract reduced body weight, food intake and fat accumulation in rats. 205.41 mg/kg and 308.25 mg/kg of standardized extract reduced adipose tissue accumulation, blood cholesterol, TG and LDL levels while increasing HDL levels in obese mice.	Reduced weight gain in overweight women who consume capsule containing 250 mg of 10% extract according to the requested dose. BMI, body weight, fat content, lean body mass and basal metabolic rate was reduced in volunteers who received 500 mg of extract (10%	Not significant	[91-98]

						compound **12**) twice a day with their meals.		
Gymnema sylvestre (Periploca of the woods, gurmar, meshashringi, madhunashini, kavali, kalikardori, dhuleti, mardashingi, adigam, cherujurinja, podapatri and sannagerasehambu)	Leaves	Gymnemic acid **16** Gymnemate	Decreases fat digestibility promoting faecal excretion, decreases food and water intake	No	100, 250 and 500 mg/kg of extract reduced body weight gain, serum lipid levels, insulin, leptin, adipose tissue and liver inflammation dose dependently. 120 mg/kg of water-soluble fraction of EtOH extract reduced body weight gain and visceral fat pad weight in obese rats. 62.5 g/kg of water extract (contain gymnemate) reduced body weight, total cholesterol, food and water intake in rats.	Reduction in body weight, BMI, serum leptin levels in obese patients who received a combination of HCA-SX plus niacin-bound chromium and standardized extract containing 25% compound **16.**	Cause liver and kidney problems at high dose	[115 ,118 - 123]
Hibiscus sabdariffa (Roselle, Karkade and Red Sorrel)	Calyces, flowers	Hydroxycitric acid **17**	Inhibition of expression of adipogenic transcription factors C/EBPα and PPARγ, reduces food intake, blocks MAPK pathway	Aqueous flower extract inhibited adipocyte differentiation of 3T3-L1 preadipocytes dose dependently. Polyphenolic extract and its fraction inhibited lipid accumulation dose dependently.	15% (dietary weight) of 96% EtOH calyx extract reduced weight gain, food intake and food efficiency in rats. 25, 50 and 100 mg of water extract reduces fat accumulation, liver cholesterol, TG levels of hamsters dose dependently.	Reduced body weight, BMI, body fat, waist circumference in males and females who consumed 450 mg aqueous flowers extract according to requested dose for 12 weeks. Reduced TG, HDL and LDL in elderly women who	None observed	[124 ,127 - 134]

						consume 2 g of aqueous calyx extract for 21 days.		
Melastoma malabathricum (Malabar melastome, Singapore rhododendron, Indian rhododendron, planter's rhododendron, phutkola, phutuka, phutki, longumpu, senduduk and yemudan)	Leaves	No	Unknown	No	5% (w/w per 100 g diest) of MeOH extract reduced body weight gain, cholesterol, LDL, HDL and total lipids, epididymal fat, retroperitoneal fat weights and phospholipid concentration.	No	None observed	[135,136,140-142]
Polygonum minus (kesum, phakphai, Kleiner Knoterich, Chakhong-machain Manipuri)	Aerial parts	No	Unknown	99.8% EtOH aerial parts extract exhibited PL inhibitory activity, IC_{50} = 40 mg/mL.	200 and 400 mg/kg of 99.8% EtOH aerial parts extract reduced weight gain and abdominal fat percentage in rats dose dependently.	No	None observed	[154,156-158]
Salvia officinalis (Common sage, garden sage, maramia)	Leaves	Carnosic acid **18** Carnosol **19** 7-Methoxyrosmanol **20** Royleanonic acid **21** Oleanolic acid **22**	Pancreatic lipase inhibition, inhibits adipocyte differentiation in 3T3-L1 cells	MeOH extract exhibited PL inhibitory, IC_{50} = 94 µg/mL. Compound **18**, **19**, **20**, **21** and **22** exhibited PL inhibitory, IC_{50} = 12, 4.4, 32, 35 and 83 µg/mL, respectively.	500 and 1000 mg/kg of MeOH extract reduced serum TG elevation in mice. Compound **18** inhibited TG elevation in mice at a dose level of 5-20 mg/kg, and also reduced the body weight gain and accumulation of epididymal fat weight	No	Neurotoxicity and convulsions of essential oil due to thujone at high dose	[159-166]

					in mice at 20 mg/kg/day.			
Sida rhomboidea, sida rhombifolia (Mahabala, Uhan, Country Mallow)	Leaves	No	Inhibit 3T3-L1 differentiation, reduces adipocytes size, decreases triglyceride accumulation and leptin release, decreases food intake, down regulated mRNA expression PPARγ2, SREBP1c, fatty acid synthase and leptin release and up-regulated carnitine palmitol transferase-1	Aqueous extract inhibited adipogenesis in 3T3L1 preadipocytes while reduced TG accumulation and leptin release.	1% (g/kg dietary weight) of aqueous extract reduced weight gain and food intake but increase plasma lipids and leptin levels, visceral fat and adipocyte hypertrophy in mice.	No	Increase plasma AST and ALT levels	[167 - 171]
Vitis vinifera	Seeds, leaves, stems, roots	Vanillic acid **23** Gallic acid **24** Syringic acid **25** *o*-Coumaric acid **26** Caffeic acid **27** Ferulic acid **28** Sinapic acid **29** Resveratrol **30** Stilbesterol **31** Ampelopsin A **32** Vitisin B **33** 3,4',5-Trimethoxy stilbene **34** Vitisin A **35**	Pancreatic lipase inhibition, inhibits lipoprotein lipase, inhibits adipogenesis, adipocyte differentiation in 3T3-L1 adipocytes, increase adiponectin, decreases serum lipids, insulin and leptin, reduces food intake, reduces PPARγ and C/EBPα, inhibits adipocyte differentiation through cell cycle arrest, activation of AMPK pathway, protects against high fat diet-induced DNA damage	Leaf extract exhibited PL inhibitory, IC_{50} = 1.18 mg/mL. Compound **23** inhibited lipid accumulation, decreased differentiation of 3T3-L1 adipocytes and suppressed adipogenic factors at concentrations of 0.1-10 μM dose dependently. 270 μM of compound **24** suppressed 3T3-L1 adipocyte hypertrophy and inflammatory mediator expression. Compound **25** inhibited differentiation of 3T3-L1 preadipocytes, reduced lipid accumulation and	400 mg/kg/day of leaf extract reduced food intake, body weight and tissue fat accumulation in obese mice. 10 and 200 mg/kg/day of compound **23** reduced body weights in obese mice. 1% (w/w dietary weight) of compound **24** reduced serum cholesterol levels and 3T3-L1 adipocyte size in obese mice**.** Compound **26** decreased body, liver organ, adipose tissue weights of peritoneal and epididymal fat pads, TG, cholesterol levels in rats at 100	Reduced body weight, BMI, waist circumference and waist to hip ratio in obese or overweight participants who received grape seed extract at 300 mg/day for 12 weeks. Lowered body weight, BMI, fat mass and waist circumference in patients who consumed 500 mg of compound **30** three times per day before meals for 90	None observed	[183 - 195]

	ameliorated ROS accumulation dose dependently. Compound **30**, **31**, **32**, **33**, **34** and **35** inhibited adipocyte differentiation with IC_{50} values of 38.4, 34.3, 25.4, 21.7, 7.7 and 5.0 μM, respectively.	mg/kg. 0.02% and 0.08% (w/w dietary weight) of compound **27** reduced body weight, visceral fat mass, gonadal fat pad mass, serum cholesterol and serum TG in mice. 200 mg/kg/day of compound **30** reduced body, WAT weight gain, WAT expansion and inflammation in obese mice.	days.

4.2. Arachis hypogaea

Arachis hypogaea is a leguminous plant of Fabaceae family that is cultivated primarily for its edible seeds and consumed worldwide. Peanuts are the seeds of this plant and contain a lot of energy and nutritional value due to the present of variety of phytonutrients, such as resveratrol, phenolic acids, isoflavonoids and phytosterols [36].

In fact, peanut shells contain a variety of useful compounds, including luteolin (**4**) (Figure 2), caffeic acid, ferulic acid, benzoic acid and certain fatty acids, all of which are known to inhibit pancreatic lipase. However, the inhibitory activity of these compounds has not been studied individually, except for luteolin [37, 38]. Shimura et al. [37] reported that luteolin showed PL inhibitory activity with an IC_{50} value of 7.1 μM. A study by Moreno et al. [38] showed that an ethanol extract of peanut shell (*A. hypogaea*) reduced glycerol release from 3T3-L1 adipocytes in an *in vitro* assay. In addition, it exhibited a dose-dependent inhibition of pancreatic lipase and a mild inhibition of lipoprotein lipase. In an *in vivo* study, high-fat diet fed rats supplemented with 1% w/w peanut shell extract gained significantly less weight than the group fed a high-fat diet alone. Furthermore, while food consumption did not differ between the two group, fecal lipid levels were higher in the treated group. However, this study lacked positive control [38].

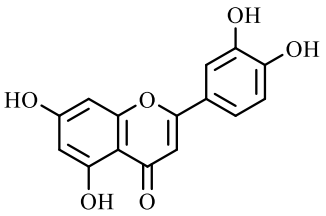


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Figure 2. Luteolin from *A. hypogaea*

Despite being classified as a high-fat and high-energy food, including peanuts in the diet does not appear to lead to weight gain. Peanuts contain primarily monounsaturated fatty acids (MUFAs), which have many benefits, such as increasing HDL levels, reducing LDL levels, and a phenomenon called diet-induced thermogenesis [39-41]. A study of lean and overweight adults investigated the effects of peanut oil intake on appetite, body composition, energy expenditure, and lipid profile [40]. Mechanisms by which peanut intake does not lead to weight gain include increased satiety, meal compensation, reduced efficiency of energy absorption, and increased energy expenditure. The studies showed that people who eat nuts have a lower body mass index than those who do not eat nuts [40, 41]. Clinical studies have shown that people who eat nuts gain less weight, and moderate-fat diets containing nuts have been shown to improve compliance and nutritional status compared with low-fat diets. These dietary patterns also lead to favorable changes in lipid profiles and reduce the risk of cardiovascular disease and type 2 diabetes [40]. Peanuts may be beneficial for weight management because they have a low glycemic index and are high in fiber [39-41]. Further research should focus on determining the optimal dose and molecular mechanism of action. However, another clinical study done by Claesson et al. [42] showed that the consumption of peanuts as snacks does not result in the same negative metabolic effects as the snacking based on candy. Significant increased body weight and waist circumference was observed in the group of snacking based on candy [42].

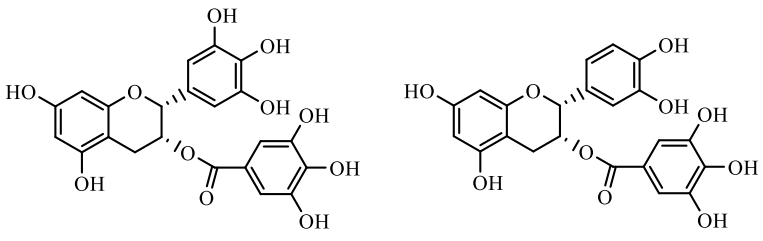
4.3. Camellia sinensis

Camellia sinensis, commonly known as green tea, belongs to the family Theaceae and is a shrub with a yellow-white flowers and light-green leaves. It is native to mainland China, South and Southeast Asia, but is now cultivated in tropical and subtropical regions around the world. There are six forms of tea: green, oolong, black, white, dark and yellow tea, each of which is made through fermentation, which changes the colour and phytochemical composition of the tea, in addition to its natural green color [43]. Green tea is a non-fermented tea made by inactivating the polyphenol oxidase

enzyme at high temperatures, thereby retaining the polyphenol content of the dried leaves. As a result, green tea is the richest in catechins compared to the other two forms [43].

This plant is reported to contain nearly 4000 bioactive compounds, one third of which are polyphenols. In addition to this group of compounds, it also contains alkaloids such as caffeine, theobromine and theophylline, amino acids, proteins, carbohydrates, chlorophyll, phenolic compounds, such as (-)-epigallocatechin-3-gallate (EGCG) (**5**), (-)-epicatechin-3-gallate (ECG) (**6**) (Figure 3), and proanthocyanidins. as well as volatile organic compounds [44]. The anti-obesity effects of green tea extract and its compounds have been extensively studied, and different mechanisms of action have been proposed. These include enhanced thermogenesis and fat oxidation due to its high caffeine content [45,46], reduced levels of leptin which regulates appetite [47], inhibition of gastric and pancreatic lipase [46, 48, 49], stimulation of the sympathetic nervous system [50], enhanced triglyceride excretion [51], reduced levels of lipoprotein lipase, hormone-sensitive lipase, and UCP2 expression [52], reduced adipocyte size and inhibited adipocyte differentiation [53, 54], increased expression of genes involved in fatty acid synthesis and oxidation [55], modulation of the intestinal microbiota [56], increased levels of adiponectin and ghrelin [57], which have been shown to contribute to weight loss in many *in vivo* studies involving animals and humans.

Choi's group reported that feeding a high fat-diet supplemented with 0.25% (w/w) green tea extract for 12 weeks improved obesity, hepatic steatosis, dyslipidemia, and insulin resistance in diet-induced obese (DIO) mice [58]. In this study, green tea extract played a role in regulating overall metabolic balance by affecting transcriptional responses related to lipid, glucose, and amino acid metabolism. Another group of researchers found that obese women lost significant weight after taking a high dose of EGCG (856.8 mg/day) [59]. In contrast, a study involving 60 Caucasian subjects found that taking green tea extract (540 mg/day EGCG) for 12 weeks while on a normal diet did not result in weight loss [60]. The authors suggested that the energy expenditure induced by catechins is related to increased fat oxidation, but that this effect may not persist with long-term green tea consumption. Studies investigating the anti-obesity effects of green tea or catechins have shown that most trials have demonstrated weight loss, and that this effect was more pronounced in Asian populations than in Caucasians [50]. Although catechins have anti-obesity activity, the weight loss may also be attributed to the caffeine content of green tea. Studies have shown that when habitual caffeine intake is high, higher catechin intake may be required to achieve significant effects [50,51]. However, it is important to recognize that tea consumption may have adverse effects. The main adverse effects documented in human studies include hepatotoxicity and gastrointestinal disturbances such as vomiting and diarrhea, especially after high-dose supplementation [61-63]. A study by Gaeini et al. [64] showed that the addition of sweeteners, milk, or other additives, as well as changes in polyphenol content, significantly affected the health benefits of tea. Therefore, further clinical studies should be conducted to determine the effects of tea by considering various factors such as gender, optimal dose, and route of administration.



5 **6**

Figure 3. Anti-obesity compounds isolated from *C. sinesis*

4.4. Capsicum annuum

Capsicum annuum, also known as red pepper, paprika, or chili pepper, belongs to the Solanaceae family and is a small shrub with blue or white flowers and berries of various colors, including red, green, and yellow, native to the northern region of South America. It is not only a medicinal plant with different pharmacological effects, but also a culinary plant due to its ability to

produce the spicy and pungent flavor of the pepper [65]. Historically, it has been used to relieve coughs, toothaches, sore throats, parasitic infections, rheumatism, and to promote wound healing [66]. It is also recognized for its uses as an antiseptic, counterirritant, appetite enhancer, antioxidant, and immunomodulator [67]. Several studies have reported that C. annuum exhibits different anti-obesity mechanisms, such as improving satiety [68], thermogenesis, fat oxidation, increasing energy expenditure [69], inhibiting lipoprotein lipase and pancreatic lipase [70,71], inhibiting adipocyte differentiation [72], preventing adipogenesis [73], activating AMPK [74], stimulating lipolysis in adipose tissue [75], and regulating the secretion of adipokines in adipose tissue [76].

A study by Baek et al. [70] showed that the green pepper water extract inhibited the activity of lipoprotein lipase (LPL) in 3T3-L1 cells. The results showed a significant decrease of the LPL mRNA expression level of up to 50.9% compared to the control group [70]. Another study conducted by Jeon et al. [77] also showed that when *C. annuum* seed extract was added to 3T3-L1 cells at concentrations of 50, 100, and 200 μg/mL from day 0 to day 6, *C. annuum* seed methanol extract exhibited excellent anti-adipogenic properties and significantly reduced the expression of important adipogenic transcription factors C/EBPβ, C/EBPα, and PPARγ compared with the control group [77]. Similarily to another study involving 3T3-L1 cells [78], the methanolic extract of *C. annuum* showed a decrease in glycerol 3-phosphate dehydrogenase (G3PD) activity.

An *in vitro* study has shown that 9-oxooctadeca-10,12-dienoic acid (**7**) (Figure 4) isolated from methanol extract of *C. annuum* can effectively slow down fat accumulation by inhibiting fatty acid biosynthesis through inhibition of acetyl-CoA carboxylase (ACC) [79]. However, the source of all materials was not determined in this study and lack of positive control. Capsaicin (**8**) (Figure 4) is the main compound in *C. annuum* and has been reported to have anti-obesity effects [76,80,81]. In a study by Leung [80], rodents supplemented with 0.014% capsaicin in their diet showed a significant decrease in visceral fat mass despite no change observed in calorie intake [80]. A 5-week study in obese rats showed that high-dose chitosan capsaicin microspheres (CCM) (3382 mg/kg/day) was superior to orlistat (75 mg/kg/day) in controlling body weight [81]. However, no rationale was provided for choosing a high dose (over 200 mg/kg/day), and therefore no relevant experimental data could be provided for further study. In one study, mice were administered capsiate (**9**) for two weeks. The result showed that oxygen consumption, carbohydrate oxidation, and fat oxidation increased significantly in the treated group. Increased oxygen consumption indicates increased calorie burning, indicating increased energy expenditure. In addition, the average body weight of the treated group decreased significantly, and the relative weight of epididymal and perirenal fat also decreased. In addition, capsiate administration inhibited abdominal fat accumulation [82]. A meta-analysis of human studies also showed that oral administration of capsaicin (**8**) and capsaicin derivatives (**9** and **10**) increased energy expenditure (245 kJ/day) and decreased the respiratory quotient by 0.216, indicating enhanced fat oxidation [83].

The toxicity of capsaicin is primarily related to its topical application, which causes a burning sensation. However, systemic toxicity following oral administration is rare. Studies in dogs using chemically synthesized pure trans-capsaicin did not show significant toxicity. Transient tachycardia (increased heart rate) and hypertension (high blood pressure) were observed, but these effects were minor because trans-capsaicin is rapidly eliminated from the body even after intravenous infusion [84]. However, excessive consumption of a mixture containing ginger, cloves, red chili pepper, and black pepper has been shown to induce hepatocellular necrosis and lead to acute hepatitis in adult rabbits. Red chili pepper alone has also been observed to cause mild swelling of hepatocytes [85]. Further investigation of its molecular mechanism of action and determination of optimal dosage are warranted.

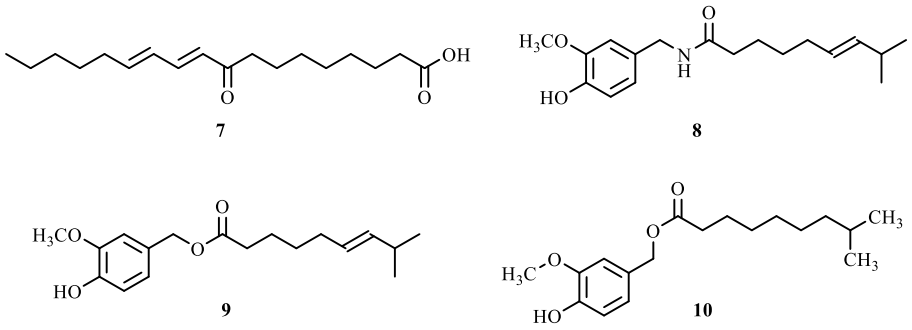


Figure 4. Anti-obesity compounds isolated from *C. annuum*

4.5. Cassia mimosoides

Cassia mimosoides is a low-growing annual or short-lived perennial plant of the Fabaceae family, commonly known as Japanese tea or tea senna, and is common in China and Japan. It has a variety of therapeutic uses, such as treating oral ulcers, diarrhea, headaches, and stomach cramps, as well as dressing wounds and sores [86,87].

A study by Heo et al. [88] showed that treatment of 3T3-L1 adipocytes with a standardized ethanol extract of *C. mimosoides* leaves inhibited lipogenesis and adipogenesis by decreasing the expression of CCAAT/enhancer binding protein-α, peroxisome proliferator-activated receptor (PPAR)-γ, sterol regulatory element binding protein-1, and fatty acid synthase, while increasing the levels of acetyl-CoA carboxylase. Oral administration of the ethanol extract for 10 weeks reduced weight gain and body fat accumulation in mice fed a high-fat diet. The extract not only attenuated lipogenesis and lipid accumulation in white adipose and liver tissues of mice, but also regulated plasma levels of insulin, leptin, and adipokines [88].

Yamamoto et al. [89] investigated the effect of a proanthocyanidin-rich aqueous ethanolic extract of the aerial parts of *C. mimosoides* (CT-II) on pancreatic lipase activity. The extract inhibited pancreatic lipase by 50% at concentrations ranging from 0.1 mg/mL to 0.071 mg/mL. Lean rats fed a high-fat diet containing 2.5% CT-II had reduced body weight, fat, and liver fat compared with rats fed a high-fat diet alone, despite similar food intake. Higher levels of dietary CT-II significantly suppressed body weight in a dose-dependent manner and reduced triglyceride levels after 14 days. In obese rats, CT-II reduced body weight and fat content, increased fecal cholesterol and fat excretion, and effectively inhibited pancreatic lipase without causing side effects such as diarrhea. Blood chemistry parameters remained normal compared with orlistat treatment. However, the underlying mechanism of CT-II's inhibition of lipase is unclear.

Five flavan dimers extracted from fruit showed inhibitory effects on pancreatic lipase. Among them, (2S)-3',4',7-trihydroxyflavan-(4α→8)-catechin (**11**) (Figure 5) exhibited the highest potency, with an IC_{50} value of 5.5 mM [90]. This study did not indicate the source of research materials and its molecular mechanism of action and was lacked a positive control. Further studies are needed to determine the optimum dose and molecular mechanism of action for pancreatic lipase inhibition. Also, clinical studies should be conducted to demonstrate any pharmacological effects.

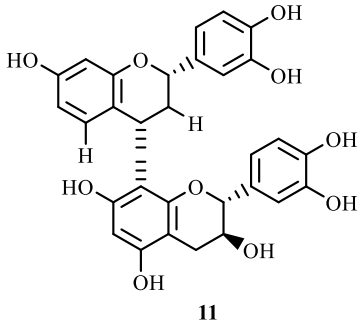


Figure 5. Anti-obesity compounds isolated from *C. mimosoides*

4.6. Coleus forskohlii

Coleus forskohlii, belongs to the Lamiaceae family and is a well-known native medicinal plant that is widely distributed in India, Nepal, Thailand and Malaysia. It has been used in traditional Ayurvedic medicine since ancient times to treat insomnia, epilepsy, eczema, psoriasis, cardiovascular disease, hypertension, bronchitis and asthma because it contains the diterpenoid compound forskolin (**12**) from the root of *C. forskohlii* (Figure 6) [91]. Forskolin (**12**) directly acts on adenylate cyclase, thereby activating cyclic adenosine monophosphate (cAMP) [92]. cAMP activation promotes the breakdown of stored fat, increases the basal metabolic rate, enhances the utilization of body fat, and regulates the thermogenic response to food [93].

Han et al. [94] observed a decrease in body weight, food intake, and fat accumulation in ovariectomized rats treated with *C. forskohlii* extract. Anzar et al. [95] also found that administration of *C. forskohlii* extract reduced adipose tissue accumulation and lowered blood cholesterol, triglyceride, and LDL levels, while increasing HDL levels in mice with high-fat diet-induced obesity. A clinical study suggested that *C. forskohlii* may help reduce weight gain in overweight women without any clinically significant side effects, but it does not appear to actively promote weight loss [93]. In one 8-week study, six overweight women administering *C. forskohlii* extract orally experienced significant reductions in body weight and fat mass and increase in muscle mass [96]. In another 8-week study conducted by Kamohara and Noparatanawong [97], 15 healthy volunteers who took an extract of *C. forskohlii* had a decrease in body mass index, weight and fat content compared to baseline after 8 weeks. However, three subjects reported abdominal discomfort, such as increased bowel movement frequency, diarrhea and soft stool [97]. Apart from increased HDL cholesterol levels, no other clinically significant side effects were observed in extensive blood and marker screening and the oral lethal dose (LD_{50}) of forskolin (**12**) was found to be 3100 mg/kg, and no detectable mutagenicity [93,98]. The molecular mechanism of action and determination of optimal dose should be studied.

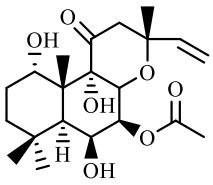


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Figure 6. Forskolin from *C. forskohlii*

4.7. Cosmos caudatus

Cosmos caudatus, also known locally as "ulam raja", "kenikir", "cosmos" or "daoruangpharma", belongs to the Asteraceae family and is an herbaceous plant with pink or purple flowers and edible leaves that have many therapeutic properties. It was originally grown in Latin America but is now cultivated around the world, including Malaysia [99]. It is often called the king of salads as it is one of the most edible leafy vegetables in Malaysia. It is used to treat infections, promote blood circulation, clear heat and other ailments [100]. Rahman et al. investigated the pancreatic lipase inhibitory activity of an ethanolic extract of *C. caudatus* leaves and found an inhibition activity of 21.7 ± 1.3% at 1000 ppm [101]. A subsequent study by the same researchers [102] showed that an ethanolic extract from *C. caudatus* leaves significantly reduced body weight gain, visceral fat mass, triglycerides and leptin levels, but increased fecal fat excretion in rats fed in high fat diet. The possible mechanism suggested is pancreatic lipase inhibition [102]. Rahman et al. found no signs of toxicity in rats [102], but another study [103] showed that the ethanol extracts of *C. caudatus* exhibited weak cytotoxic activity against P388 murine leukemia cells with an IC_{50} value of 25 µg/mL [103]. Furthermore, another study using male rats showed that a high dose of 2000 mg/kg of the aqueous extract had acute hepatotoxic effects [104]. Further studies are needed to identify the active ingredients, the detailed mechanism of action, and determine the optimal dose. Furthermore, only clinical studies can provide evidence of any pharmacological effects in humans.

4.8. Curcuma longa

Curcuma longa, commonly known as turmeric, belongs to the Zingiberaceae family and is a flowering plant native to southwestern India. The rhizome of turmeric is the source of a popular yellow spice that is widely used for its medicinal properties, such as the treatment of diabetes, inflammation, microbial infections, cancer, arthritis, anorexia, cough, sinusitis, diabetic wounds, muscle disorders, biliary disorders, and liver diseases [105]. Curcumin (**13**) (Figure 7), one of the main components of turmeric, has been reported to exhibit anti-obesity effects by regulating lipolysis [106], lipogenesis [107, 108], and inflammation [109, 110]. However, the low bioavailability and limited systemic absorption of curcumin have hampered its clinical application.

An *in vivo* study proposed mechanisms of action for curcumin such as blocking adipokine-induced angiogenesis, inhibiting 3T3-L1 cell differentiation, enhancing oxidation and fatty acid esterification, and reducing the expression of essential transcription factors [108]. Similar to other traditional FAS inhibitors, curcumin impeded 3T3-L1 cell differentiation, thereby reducing lipid accumulation. In addition, curcumin reduced FAS expression during adipocyte differentiation and decreased the mRNA levels of PPARγ and CD36 [107]. Kobori et al. [111] found that curcumin did not significantly reduce weight gain or fat accumulation in the liver and hepatic tissue, but it significantly reduced non-fasting blood glucose levels in mice fed a Western diet and reduced oxidative stress markers in the liver and epididymal white adipose tissue. However, curcumin reduced the size of individual adipocytes in epididymal white adipose tissue. In addition, it significantly suppressed the accumulation of macrophages. A curcumin mixture consisting of 73.4% curcumin (**13**), 16.1% demethoxycurcumin (**14**), and 10.5% bisdemethoxycurcumin (**15**) (Figure 7) at concentrations of 0.2% and 1% fed to rats fed a high-fat diet inhibited triglyceride accumulation in the liver, reduced weight gain in epididymal adipose tissue, and decreased plasma levels of very low-density lipoprotein triglycerides [112]. The ethyl acetate fraction from the methanol extract of *C. longa* partially inhibited lipogenesis in 3T3-L1 adipocytes by decreasing the expression of GLUT-4 [113]. In addition, it promoted lipolysis by inducing the expression of HSL and/or ATGL genes, thereby increasing glycerol release [113]. Turmeric and curcumin are neither mutagenic nor genotoxic. Oral administration of turmeric and curcumin at specific doses did not cause reproductive toxicity in animals. Human studies have shown that oral administration of 6 g/day of curcumin for 4 to 7 weeks did not produce toxic effects and is therefore considered safe. Of note, curcumin may be only poorly absorbed in the gastrointestinal tract and may cause some adverse effects, such as gastrointestinal discomfort. However, bioavailable preparations of curcumin have not shown significant toxicity in both animals and humans [114]. Further studies are needed to confirm these findings and better understand this issue.

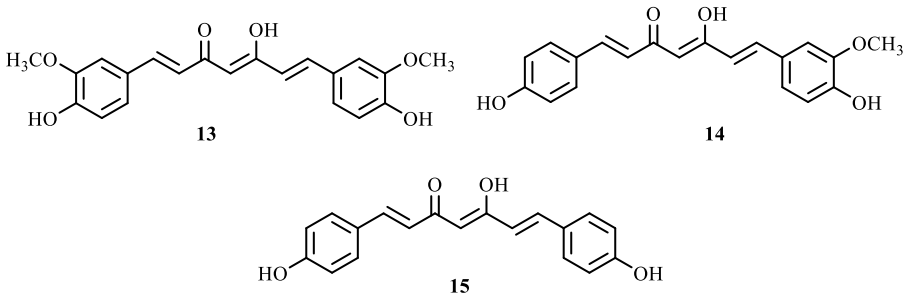

Figure 7. Anti-obesity compounds isolated from *C. longa*

4.9. Gymnema sylvestre

Gymnema sylvestre has many names including gymnema, gurmar, meshashringi, madhunashini, kavali, kalikardori, dhuleti, mardashingi, adigam, cherujurinja, podapatri, and sannagerasehambu [115]. It is a perennial woody climbing shrub belonging to the Asclepiadaceae family, native to India. It has been used for decades to treat eye diseases, asthma, diuresis, anemia, family planning, snake bites, stomach problems, urinary tract diseases, chronic cough, hemorrhoids,

dyspnea, chronic cough, heart disease, colic, constipation, hemorrhoids, and indigestion [116, 117]. It has also been found to inhibit the perception of sweet tastes due to its effects on the taste buds of the tongue, resulting in a decreased ability to taste sweet and bitter flavors. This effect is thought to be related to gymnemic acid (**16**) (Figure 8) and gurmarin (a type of peptide), which may help to reduce the intake of sugary foods [118].

Kim et al. [119] investigated the effects of *G. sylvestre* extract on mice fed a high-fat diet and found that the extract significantly reduced body weight gain, serum lipid levels, insulin, leptin, and inflammation in adipose tissue and liver. In addition, *G. sylvestre* extract in different doses of 100, 250 and 500 mg/kg body weight exhibited hypoglycemic effects by inhibiting amylase activity. Notably, a dose range of 100-200 mg/kg for an *in vivo* study of extracts should be considered as being the upper limit for a meaningful pharmacological study [31]. Another study showed that the water-soluble fraction of the ethanol extract of *G. sylvestre* significantly reduced body weight gain and visceral fat pad weight in obese rats fed a high-fat diet [120]. According to an *in vivo* study by Luo et al. [121], gymnemate were fed to rats with progressive obesity, hyperlipidemia, and hyperglycemia. The results showed that these rats had a decrease in body weight, food and water consumption, and improved lipid profile, including a decrease in low-density lipoprotein and very low-density lipoprotein levels.

A clinical study using a combination of (-)-hydroxycitric acid, niacin-bound chromium, and *G. sylvestre* extract in moderately obese patients showed a 6.1% reduction in body weight and BMI, compared to a 5% reduction in BMI in patients taking (-)-hydroxycitric acid alone. Serum leptin levels were reduced by 44.3% and 39.2%, respectively, in these two groups. It is unclear whether the greater weight loss observed was due to the presence of the combination of *G. sylvestre*, niacin-bound chromium, or the effectiveness of the combination of these elements [122]. An acute and subacute toxicity study in rats using crude extracts and fractions of the plant showed that subacute doses of 300 and 600 mg/kg body weight may be harmful to the liver and kidneys. Therefore, oral doses of *G. sylvestre* of 100 mg/kg or less are recommended [123]. Further studies should focus on elucidating the molecular mechanism of action and the optimal dose

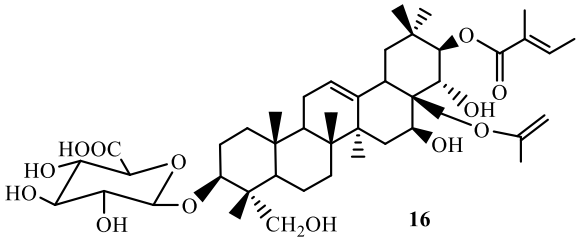

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Figure 8. Anti-obesity compounds isolated from *G. sylvestre*

4.10. Hibiscus sabdariffa

Hibiscus sabdariffa, also known as Roselle, kakad flower, and Red Sorrel, belonging to the family of Malvaceae is a shrub with red edible calyces and native to Angola in Africa but now grown in India, China, Mexico, North Africa, Malaysia and Thailand. In the old days, it was used as a diuretic, laxative, cholerectic, febrifugal, hypotensive, antibacterial agent and antifungal agent [124]. Besides, it can be used to treat sore throats, coughs, genital problems, liver disorders, high blood pressure, cardiac and nerve diseases [124-126].

Several studies have shown that *H. sabdariffa* has anti-obesity effects both *in vitro* and *in vivo* [127-132]. In an *in vitro* study, an aqueous extract of *H. sabdariffa* not only dose-dependently reduced cytoplasmic lipid accumulation by 46.6% (at a concentration of 2 mg/mL) but also decreased the expression of leptin mRNA and transcription factors (C/EBPa and PPARg). Furthermore, the reduction in lipid accumulation led to the inhibition of the insulin signaling cascade (PI3-K), and the MAPK pathway in adipocyte differentiation was also blocked. In an earlier study, the same researchers showed that Hibiscus sabdariffa extract directly inhibited cytoplasmic lipid accumulation and adipogenic differentiation of preadipocytes [127,128].

Another group of researchers found that the group of rats that received the highest dose of ethanolic extract of calyx (15 g per 100 g diet) had a significant decrease in weight gain, food intake, and food efficiency compared to the control group [129]. They suggested that the reduction in food intake may be related to palatability issues, while the anti-obesity effect may be due to the inhibition of α-amylase and pancreatic amylase, possibly due to the presence of hydroxycitric acid (**17**) (Figure 9). Meanwhile, the lowest dose group (5 g per 100 g diet) had a significant increase in fatty acid excretion, but no significant weight loss [129]. *H. sabdariffa* polyphenolic extract can dose-dependently reduce the effects of high-fat diet in hamsters [130]. In addition, it can inhibit adipogenesis in adipocytes [131]. Clinical studies have demonstrated that *H. sabdariffa* extract and its tea can help people aged 18-65 years and elderly women lose weight, respectively [132,133]. *H. sabdariffa* is considered safe food as no side effects or adverse reactions have been reported [134]. Further study is needed to investigate its molecular mechanism of action and determine the optimum dose.

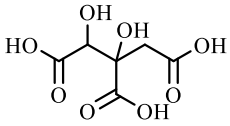

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Figure 9. Hydroxycitric acid from *H. sabdariffa*

4.11. Melastoma malabathricum

Melastoma malabathricum, also known as *Malabar melastome*, Singapore rhododendron, Indian rhododendron, planter's rhododendron, phutkola, phutuka, phutki, longumpu, senduduk and yemudan, is a medicinal plant with purple, pink or white flowers belonging to the family Melastomataceae, native to tropical and temperate Asia and the Pacific Islands, but now also found in Southeast Asia such as Malaysia [135]. *M. malabathricum* has traditionally been used in Malaysia, Indonesia and India for its miraculous healing properties in the treatment of diarrhea, dysentery, inflammation, hemorrhoids, cuts and wounds, toothache, stomachache, oxidative stress, microbial infections and cancer [136-139].

The methanolic extract of *M. malabathricum* leaves prevented the increment in body weight, cholesterol, LDL, HDL and total lipids of high-fat diet fed rat group with treatment [140]. In addition, a decrease in epididymal fat, retroperitoneal fat weights and phospholipid concentration induced by high-fat diet was found [140]. A 14-day *in vivo* acute toxicity study showed that the ethanol extract of *M. malabathricum* was safe even at a high dose of 5000 mg/kg, and did not exhibit any oral toxicity [141]. Another recent acute and subacute dermal toxicity study showed that the ethanolic extract of *M. malabathricum* leaves did not exert acute and subacute adverse effects on skin or systemic toxicity reaction in rats [142]. Further studies are needed, such as validating the optimal dose, active ingredients, and a mechanism of action. In addition, clinical studies should be conducted to demonstrate any pharmacological effects.

4.12. Phaseolus vulgaris

Phaseolus vulgaris, also known as white kidney bean or common bean, is an annual herbaceous plant in the family Fabaceae, native to tropical America but now cultivated worldwide. It has small white or pink flowers and kidney-shaped seeds in narrow rectangular pods. It has been one of the most valued foods in Mexican culture since pre-Hispanic times, recognized for its nutritional qualities as a source of protein, fiber, calcium, and iron [143]. Polyphenols are the main bioactive components of various common beans and have a variety of biological activities, including anti-obesity properties. Shi et al. [144] reported that ethanolic extract of common bean which is rich in polyphenol could inhibit 3T3-L1 adipocytes differentiation. The extract reduced lipid content in the mature adipocytes to 79.29% at 150 μg/mL and 35.13% at 300 μg/mL. In addition, the extract also suppressed the mRNA expression level and the protein expression level of peroxisome proliferator-

activated receptor γ (PPARγ), CCAAT-enhancer-binding protein α (C/EBPα), sterol-regulatory element binding proteins 1 c (SREBP-1c), lipoprotein lipase (LPL), and fatty acid binding protein. An *in vivo* study using young growing rats showed that oral administration of low or moderate doses of the kidney bean lectin, phytohemagglutinin (PHA), up to 0.2 g/kg body weight/day, resulted in decreased body and skeletal muscle weight [145]. The attachment of phytohemagglutinin to stomach epithelial cells and the brush border membrane of the small intestine, cecum, and colon triggers the release of cholecystokinin and glucagon-like peptides [146]. This process reduces appetite, thereby reducing energy intake and leading to weight loss. Another *in vivo* study stated that α-amylase inhibitor enriched aqueous extract from white common bean seeds could reduced body weight gain of high fat diet-induced obese rats [147]. Several clinical trials have been conducted on kidney bean extracts [148-151]. A 12-week clinical trial showed that taking *P. vulgaris* aqueous extract in conjunction with a balanced diet and exercise resulted in significant reductions in body weight, BMI and fat mass in male and female participants with a BMI of 25 to 34.9 kg/m^2 [148]. Their results suggest that the weight loss effect is based on the inhibition of α-amylase (an enzyme necessary for the digestion of carbohydrates) by the natural α-amylase inhibitor (also known as starch blocker) phaseolamin in kidney bean extract, thereby reducing carbohydrate digestion and absorption [152,153]. Another 60-day clinical trial tested 101 volunteers with a BMI between 25 and 40 and showed that the active group experienced significant weight loss and decreased waist measurement compared to the placebo group [150]. Importantly, no adverse side effects have been reported [148-151]. Further research is needed, such as identification of the active components and the determination of the optimum dose.

4.13. Polygonum minus

Polygonum minus, commonly known as kesum, phakphai, Kleiner Knoterich or Chakhong-machain Manipuri, is a tropical herb with edible leaves native to Southeast Asian countries, particularly Malaysia, Thailand, Vietnam and Indonesia [154]. In addition to being used as a flavoring agent for its sweet and pleasant aroma, it is also a traditional medicine for a variety of ailments, including fungal infections, vision problems, and body pain [155]. Arshad et al. [156] evaluated the anti-obesity potential of aerial parts of *P. minus* in vitro and in vivo. In an *in vitro* study with Orlistat as a control, the IC_{50} value of *P. minus* harvested at 12 weeks against pancreatic lipase was 40 mg/mL, but Orlistat showed a relatively better IC_{50} value. Their results showed that ethanol extract of *P. minus* harvested at 12 weeks could reduce weight gain and abdominal fat percentage in rats. However, the potential mechanism of action leading to weight loss is not well investigated. They stated that the reduction in weight gain was not primarily related to inhibition of pancreatic lipase in the gastrointestinal tract in vivo or any significant changes in food and calorie consumption patterns, thus suggesting that other factors may also play a role in the observed reduction in weight gain. In addition, acute oral toxicity evaluation of *P. minus* extracts showed no mortality or clinical signs of toxicity in rats [156]. Other studies also supported safe consumption of natural products from *P. minus* [157,158]. Further research on this plant is needed to reveal its active components, optimal dosage and mechanism of action. Only clinical studies can provide evidence of any pharmacological effects in humans.

4.14. Salvia officinalis

Salvia officinalis, also known as common sage, garden sage or maramia, is an aromatic medicinal shrub in the Lamiaceae family with blue-purple flowers and white leaves. It is native to the Mediterranean region but is now grown throughout the world [159]. It is widely used in traditional medicine and cooking. In traditional medicine, it has been used to treat epilepsy, ulcers, gout, rheumatism, skin and throat inflammation, dizziness, tremors, paralysis, diarrhea, high blood sugar, and mild indigestion [160]. Sage is used to make herbal teas and infusions for its unique aroma. Its essential oil and various phytochemical constituents, including α-thujone, β-thujone, camphor, 1,8-cineole, and phenolic compounds such as caffeic acid, carnosic acid (**18**), carnosol (**19**), and

rosmarinic acid, play important roles in its wide range of biological activities [161–163]. Carnosic acid (**18**) and carnosol (**19**) are examples of phenolic diterpenes that are known to protect against obesity (Figure 10).

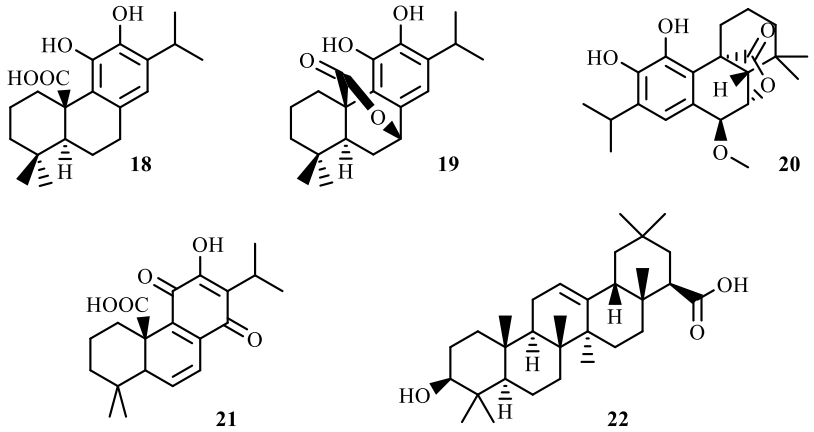

Figure 10. Anti-obesity compounds isolated from *S. officinalis*

An *in vivo* study has shown that the methanol leaf extract of this plant able to inhibit pancreatic lipase (IC_{50} = 94 mg/mL) and significantly reduced serum triglyceride levels in mice fed an olive oil diet. Subsequently, four abietan-type diterpenes (carnosic acid (**18**), carnosol (**19**), 7-methoxyrosmanol (**20**) and royleanonic acid (**21**)), and a triterpene (oleanolic acid (**22**)) were isolated and tested separately. Carnosic acid (**18**) and carnosol (**19**) exhibited the strongest pancreatic lipase inhibition with IC_{50} values of 12 mg/mL and 4.4 mg/mL, respectively. In contrast, 7-methoxyrosmanol (**20**) (IC_{50} = 32 mg/mL), royleanonic acid (**21**) (IC_{50} = 35 mg/mL), and oleanolic acid (**22**) (IC_{50} = 83 mg/mL) showed lower levels of inhibition. Notably, only carnosic acid (**18**, at doses of 5–20 mg/kg) significantly inhibited the increase in serum triglycerides after oral administration of olive oil and resulted in reduced body weight gain and epididymal fat accumulation in mice fed a high-fat diet after adminstion at a dose of 200 mg/kg to for 14 days [164]. However, only two independent sets of i*n vitro* experiments (n = 2) were performed in the study and thus impaired the validity of the findings. The analysis of three or more independent replicates is needed to reflect the validity of the observation [165]. Carnosic acid (**18**) and carnosol (**19**) also inhibited adipocyte differentiation in 3T3-L1 cells. Although *S. officinalis* essential oil has been recognized for its neurotoxic effects, which have been attributed to its presence of thujone, the toxicity of carnosic acid (**18**) and carnosol (**19**) remain unclear. A recent toxicity study reported a no-adverse-effect level of 1000 mg/kg for *S. officinalis* essential oil in female rats [166]. Further investigation of the exact mechanism of action and optimal dose is needed. In addition, clinical studies on the anti-obesity effects of this plant are lacking.

4.15. Sida rhomboidea

Sida rhomboidea, also known as *sida rhombifolia*, and commonly named as Mahabala, Uhan or Country Mallow, is a tropical shrub in the Malvaceae family that is widely used in northeastern India to relieve the symptoms of diabetes and obesity [167,168]. It is traditionally used to treat heart diseases, fever, cardiovascular diseases, urinary disorders, burning sensations, piles and all types of inflammation [169]. Studies by Thounaojam et al. [170, 171] showed that *S. rhomboidea* leaf extract inhibited adipogenesis in 3T3L1 preadipocytes and reduced triglyceride accumulation and leptin release. In mice fed a high-fat diet, the extract prevented weight gain and increased plasma lipid and leptin levels, visceral fat, and adipocyte hypertrophy. It also reduced food intake, downregulated mRNA expression of PPARγ2, SREBP1c, FAS, and leptin, and upregulated CPT-1 in epididymal adipose tissue. Acute and subchronic toxicity studies showed no major behavioral or toxic effects, no abnormalities or deaths at doses up to 5000 mg/kg. However, a dose of 3000 mg/kg resulted in

elevated AST and ALT levels. Further studies are needed to identify the active ingredients, determine the optimal dose, and conduct clinical trials.

4.16. Taraxacum officinale

Taraxacum officinale, also known as dandelion, is an edible herb in the Asteraceae family, with single yellow flowers and cotton-like fruits containing many seeds that are easily dispersed by the wind. It is native to Europe but is now grown throughout the world and used in salads [172]. It has traditionally been used as a remedy for diabetes, kidney disease, diuretic, bacterial infections, and diseases of the spleen, kidneys, and liver [173]. González-Castejón et al. [174] reported *T. officinale* leaf and root extracts could inhibit 3T3-L1 preadipocyte differentiation and reduce triglycerides content in adipocytes during 3T3-L1 adipogenesis. Zhang et al. [175] investigated the inhibitory effects of the ethanol extract on pancreatic lipase. They found that the *in vitro* inhibition rate was significantly lower at lower concentrations, but at 250 mg/mL, the extract had an inhibition rate of 86.3%, while Orlistat had an inhibition rate of 95.7% [175]. The IC_{50} values were 78.2 μg/mL for the extract and 0.22 μg/mL for Orlistat. In an *in vivo* experiment, the extract significantly reduced the plasma triglyceride levels in the test group at 90 and 180 minutes compared to the control group, indicating its potential as a pancreatic lipase inhibitor [175]. Both the *in vitro* studies by González-Castejón et al. were not pharmacologically relevant as the dose level used in the study was 300 – 600 μg/mL. For a meaningful pharmacological study, a dose range of 100 - 200 μg/mL for an *in vitro* study of extracts should be assumed as being the upper limit [31]. Based on toxicity studies, no adverse effects were reported during the consumption of dandelion extract, and it is therefore considered safe [176]. However, the authors did not indicate the animal strain and source of the substance. Furthermore, oral administration of dandelion water extract to mice at doses of 100, 250, 300, 500, and 750 mg/kg was found to be safe throughout the study. Moreover, the mice showed good prognosis in terms of associated lesions, indicating that these doses were within the safe range [177,178]. The optimal dose needs to be determined, and the detailed molecular mechanisms elucidated. Further studies are needed to identify the compounds responsible for the inhibition. Furthermore, no clinical studies have been demonstrated for the anti-obesity effects of this plant.

4.17. Vitis vinifera

Vitis vinifera, also known as grapevines, are deciduous climbing shrubs in the family Vitaceae with tendrils and edible fruit. They are native to the Mediterranean region, western Asia, and southern Europe, but are now grown in most temperate regions of the world, including Malaysia. There are more than 10,000 varieties of grapes grown worldwide. Grapes have traditionally been used in medicines such as carminatives, laxatives, anemia, allergies, wound care, bronchitis, colds, and flu [179–182].

In vitro experiments showed that *V. vinifera* leaf extract inhibited pancreatic lipase in a concentration-dependent manner with an IC_{50} of 1.18 mg/mL, but Orlistat had a better IC_{50} value of 0.21 mg/mL [183]. *In vivo* experiment, *V. vinifera* leaf extract reduced food intake, body weight and tissue fat accumulation in obese mice [183]. However, the rationale for the selection of high *in vitro* doses (more than 200 μg/mL) was not given, thus unable to provide relevant experimental data for further investigation. A total of 13 compounds was shown to have anti-obesity effects, including vanillic acid (**23**), gallic acid (**24**), syringic acid (**25**), o-coumaric acid (**26**), caffeic acid (**27**), ferulic acid (**28**), sinapic acid (**29**), resveratrol (**30**), stilbesterol (**31**), ampelopsin A (**32**), vitisin B (**33**), 3,4',5-trimethoxy stilbene (**34**) and vitisin A (**35**) (Figure 11).

Previous studies have shown that these phenolic acids may have different mechanisms of action for the treatment of obesity, such as by activating the AMPK pathway [184], preventing high-fat diet-induced DNA damage [185,186], inhibiting adipogenesis and promote lipolysis in adipocytes [187-189], down-regulating serum lipids, insulin and leptin [190], suppression of lipogenic enzymes and hepatic lipid accumulation [191], regulating lipolytic activity [192]. In another study, six isolated compounds were found to inhibit the differentiation of 3T3-L1 adipocytes. These include resveratrol (**30**) (IC_{50} = 38.4 μM), stilbesterol (**31**) (IC_{50} = 34.3 μM), ampelopsin A (**32**) (IC_{50} = 25.4 μM), vitisin

B (**33**) (IC_{50} = 21.7 μM), 3,4,5-trimethoxystilbene (**34**) (IC_{50} = 7.7 μM), and vitisin A (**35**) (IC_{50} = 5.0 μM) (**Figure 20**). Among them, vitisin A (**35**) demonstrated the strongest anti-adipogenic effect, reducing the expression of PPARγ and C/EBPα, and inhibiting adipocyte differentiation through cell cycle arrest [193]. Recent clinical studies have demonstrated that the grape seed extract and isolated compounds like resveratrol (**30**) have anti-obesity properties and could be used to treat obesity [194,195]. No adverse effects have been reported [195]. To our knowledge, the optimal dose has not yet been established.

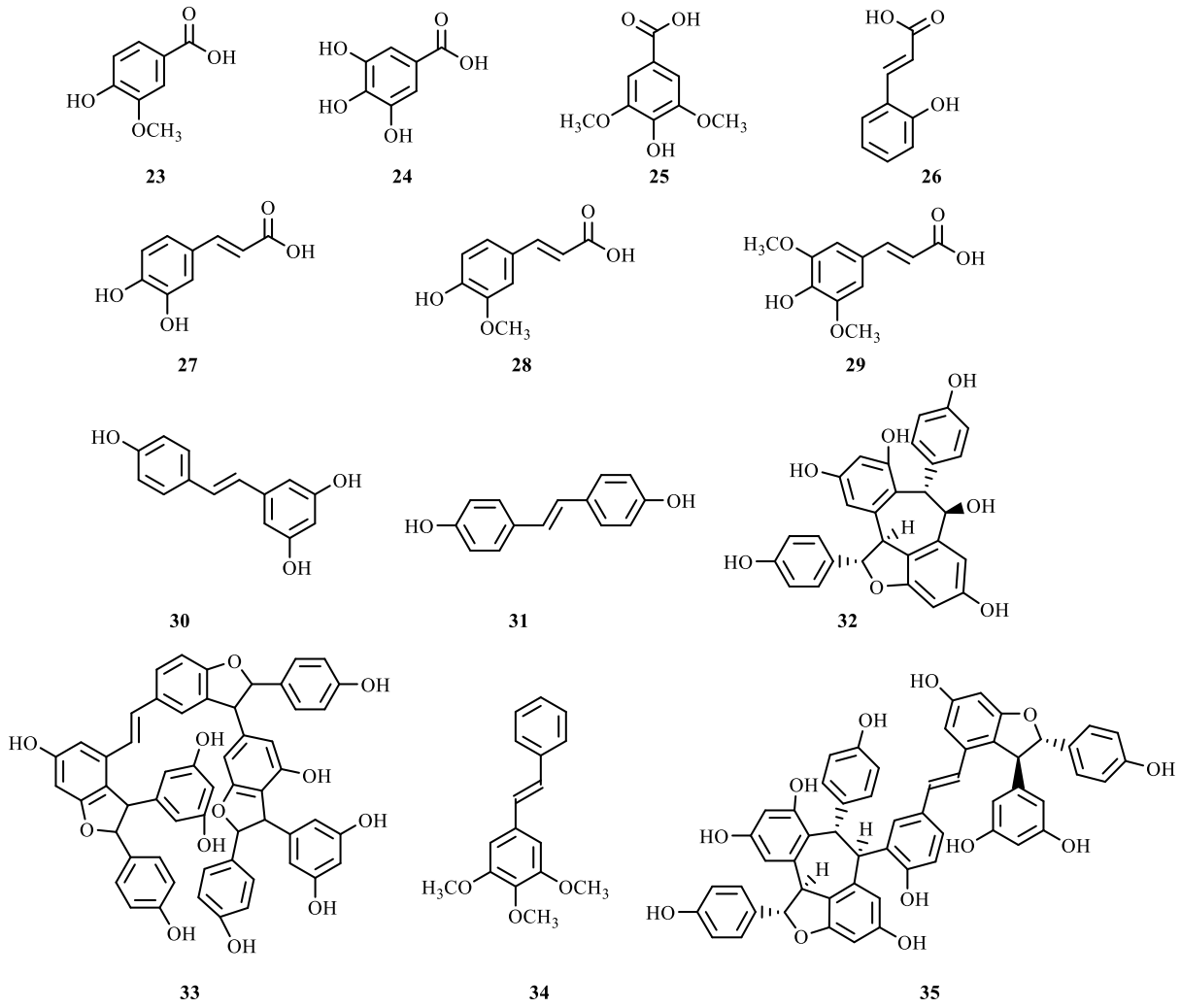

Figure 11. Anti-obesity compounds isolated from *V. vinifera*

5. Conclusions and Future Perspective

Obesity is a global epidemic that affects public health, the economy, and society, requiring urgent attention and action. This article explores the anti-obesity properties of Malaysian shrub plants studied to date *in vitro* and *in vivo* and their toxicological profiles, with the aim of providing a reference for future research and development.

Despite advances in plant research, major gaps remain in the study of herbaceous and shrub species in Malaysia. Many plants lack thorough clinical evaluation, and their ecological roles, benefits, and unique properties remain underexplored, limiting their potential applications in medicine, agriculture, and conservation. In addition, there is a lack of molecular-level studies, which require the isolation and analysis of individual compounds to better understand their specific effects. This could help improve treatments, increase efficacy, or minimize side effects. In addition, the mechanisms

underlying the anti-obesity effects of natural products are poorly understood. While preclinical studies show promise, the exact pathways and differences in individual responses complicate conclusions about their efficacy.

Comprehensive clinical research is essential to elucidate molecular mechanisms and ensure effective, evidence-based obesity interventions. As herbal and dietary supplements become increasingly popular, it is equally important to understand their safety profile. Bioactive compounds in natural products may have powerful benefits but may also present risks of toxicity or adverse drug interactions. It is critical to prioritize toxicology studies during drug discovery and development. Addressing these research gaps is essential for sustainable development, preserving plant diversity, and discovering new Malaysian plants with potential anti-obesity effects. These efforts may lead to more effective formulations and treatments for clinical applications in the fight against obesity.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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