Molecular Biology Reports (2021) 48:743–761
https://doi.org/10.1007/s11033-020-06036-8

REVIEW

Molecular mechanism of down-regulating adipogenic transcription factors in 3T3-L1 adipocyte cells by bioactive anti-adipogenic compounds

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Received: 21 August 2020 / Accepted: 25 November 2020 / Published online: 4 December 2020

Abstract

Obesity is growing at an alarming rate, which is characterized by increased adipose tissue. It increases the probability of many health complications, such as diabetes, arthritis, cardiac disease, and cancer. In modern society, with a growing population of obese patients, several individuals have increased insulin resistance. Herbal medicines are known as the oldest method of health care treatment for obesity-related secondary health issues. Several traditional medicinal plants and their effective phytoconstituents have shown anti-diabetic and anti-adipogenic activity. Adipose tissue is a major site for lipid accumulation as well as the whole-body insulin sensitivity region. 3T3-L1 cell line model can achieve adipogenesis. Adipocyte characteristics features such as expression of adipocyte markers and aggregation of lipids are chemically induced in the 3T3-L1 fibroblast cell line. Differentiation of 3T3-L1 is an efficient and convenient way to obtain adipocyte like cells in experimental studies. Peroxisome proliferation activated receptor γ (PPARγ) and Cytosine-Cytosine-Adenosine-Adenosine-Thymidine/Enhancer-binding protein α (CCAAT/Enhancer-binding protein α or C/EBPα) are considered to be regulating adipogenesis at the early stage, while adiponectin and fatty acid synthase (FAS) is responsible for the mature adipocyte formation. Excess accumulation of these adipose tissues and lipids leads to obesity. Thus, investigating adipose tissue development and the underlying molecular mechanism is important in the therapeutical approach. This review describes the cellular mechanism of 3T3-L1 fibroblast cells on potential anti-adipogenic herbal bioactive compounds.

Keywords Adipocyte · 3T3-L1 fibroblast · Anti-adipogenic activity · Bioactive herbal compounds · Obesity

Introduction

Excess energy consumption is stored in the adipose tissue of the human body. Fat acts as energy storage, and it is released as fatty acid into the bloodstream and is used as an energy source by other body tissue. Adipose tissue is therefore considered important energy storage for humans. The human body consists of two different adipose tissues, such as brown and white adipose tissue. White adipose tissue in the form of triglycerides is the most effective source of energy. In

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contrast, brown adipose tissue is responsible for energy regulating thermogenesis in the cold and hot environment [1]. Obesity is a common cause of multiple diseases, including type 2 diabetes, hypertension, and cardiovascular disease. These are all mainly associated with the increased white adipose tissue, which alters normal energy homeostasis by disturbing hormones and adipokines. The rate of obesity is growing globally, making it a significant barrier to health. Adipokines secretion interferes with insulin signaling and causes insulin production demand, leading to insulin resistance. Insulin resistance is correlated with obesity and type 2 diabetes [2, 3]. Under normal circumstances, β-cells of the pancreatic islet increase insulin release to overcome the decreased effectiveness of insulin action, retaining normal glucose tolerance. Non-esterified fatty acids impair the function of β-cells and are accelerated under obese conditions. In relation to adipocytes condition, Interleukin 6 (IL-6), Tumor necrosis factor α (TNF-α), chemoattractant, monocytes, different macrophage, and adipose tissue may also play a significant role in the formation of insulin resistance [4].

Adipogenesis is the transformation of fibroblast into adipocytes from preadipocyte. A multi-phase process was followed in adipogenesis. Depending on the adipogenesis level, the expression pattern of transcripts and protein involved in adipogenesis was organized. Different transcription factors are activated, including C/EBP α and PPARγ into adipocytes. Without these components, precursor cells cannot be distinguished into mature adipocytes. Also, PPARγ is capable of encouraging adipogenesis in C/EBP deficient cells. Based on the stage of adipogenesis, the pattern of expression of transcripts and protein engaged in adipogenesis was coordinated. Sterol regulatory element binding proteins (SREBP) is a transcription factor and a supplementary adipogenesis regulator involved in lipid metabolism and regulates FAS [5]. These transcripts and proteins control the differentiation of adipocytes are considered to be the key early adipogenesis regulators, whereas fatty acid binding protein 4 (FABP4), adiponectin, IL-6, leptin, glucose transporter type 4 (GLUT4), cluster of differentiation 36 (CD36), and insulin receptor substrate (IRS1) which are responsible for adipocyte formation. Adipocyte specific genes such as FAS, FABP4, and acetyl-coenzyme A carboxylase (ACC) decide the later adipocyte differentiation stages, and the related fatty acids and triglycerides biosynthesis are regulated by SREBP, PPARγ, and C/EBPα [6].

The in vivo study of preadipocyte differentiation is complicated, as human and animal fat tissues at various development stages combined with small blood vessels, nerve tissue, and fibroblasts. Therefore, the molecular mechanism of adipogenesis is intensively studied in vitro using different preadipocyte clonal cell lines from mice or rats. The 3T3-L1 cell line is a well-characterized and reliable model for studying preadipocyte conversion into adipocytes. Plant-derived pure compounds are evaluated for anti-adipogenic activity using in vitro methods that can control obesity and insulin resistance, leading to type 2 diabetes, and research proved its activity on the 3T3-L1 cells model. The earliest known form of human health care was herbal medicine. The herbal medicines are known to folk peoples as a remedy for various diseases. A large portion of the plant's medicinal properties appears to have developed through wild animal trials, observations, and errors. It has been an important part of the growth of modern civilization. The pharmaceutical industry currently conducted expensive research on plant materials from the rain forests and elsewhere for their possible health beneficial values [7].

Glycosides, flavonoids, alkaloids, and terpenoids are the main groups of phytochemicals that enhance anti-adipogenic activity. Medicinal plants possess these phytochemicals compounds that act through various metabolic and cellular targets on beneficial action for obesity. In clinical studies, it has been demonstrated that natural products can minimize body weight, fasting blood glucose levels, and improve insulin resistance in animal models [8]. This review article deals with information on various herbal bioactive compounds on the mechanism of anti-adipogenic property in the 3T3-L1 cell line model.

Overview of 3T3-L1 cell line

Adipocytes are produced from mesenchymal stem cells through the process of adipogenesis. Altering the level of the adipocyte cell proliferation was the major research domain in adipogenesis. The 3T3-L1 cell line was isolated and expanded from murine Swiss 3T3 cells and is a well-established pre-adipose cell line. The 3T3-L1 cells are derived from disaggregated Swiss 3T3 mouse embryos aged 17–19 days that exhibit a fibroblast-like morphology that can acquire an adipocyte-like phenotype under suitable conditions. This cell line was standardized as a model for the study of adipogenesis. The 3T3-L1 adipocyte morphology increases due to triglyceride synthesis and lipid accumulation and gains the adipose cell signet ring appearance. These cells are also susceptible to lipogenic and lipolytic hormones and drugs such as epinephrine, isoproterenol, and insulin. The 3T3-L1 cell line was maintained in the Dulbeccos modified eagle medium. It was stimulated due to 0.5 mM methyl isobutyl xanthine, dexamethasone, and 0.1 μg/ml bovine insulin and 10% fetal bovine serum for differentiation, and these cultures attained adipocyte characters (Fig. 1). The most noticeable of these modifications lead to the accumulation of lipid droplets in 3T3-L1 adipocyte, and within 10–12 days, the complete differentiation of 3T3-L1 cells was achieved [9]. Furthermore, the 3T3-L1 cell line is a useful model for testing intracellular transport, anti-adipogenesis,

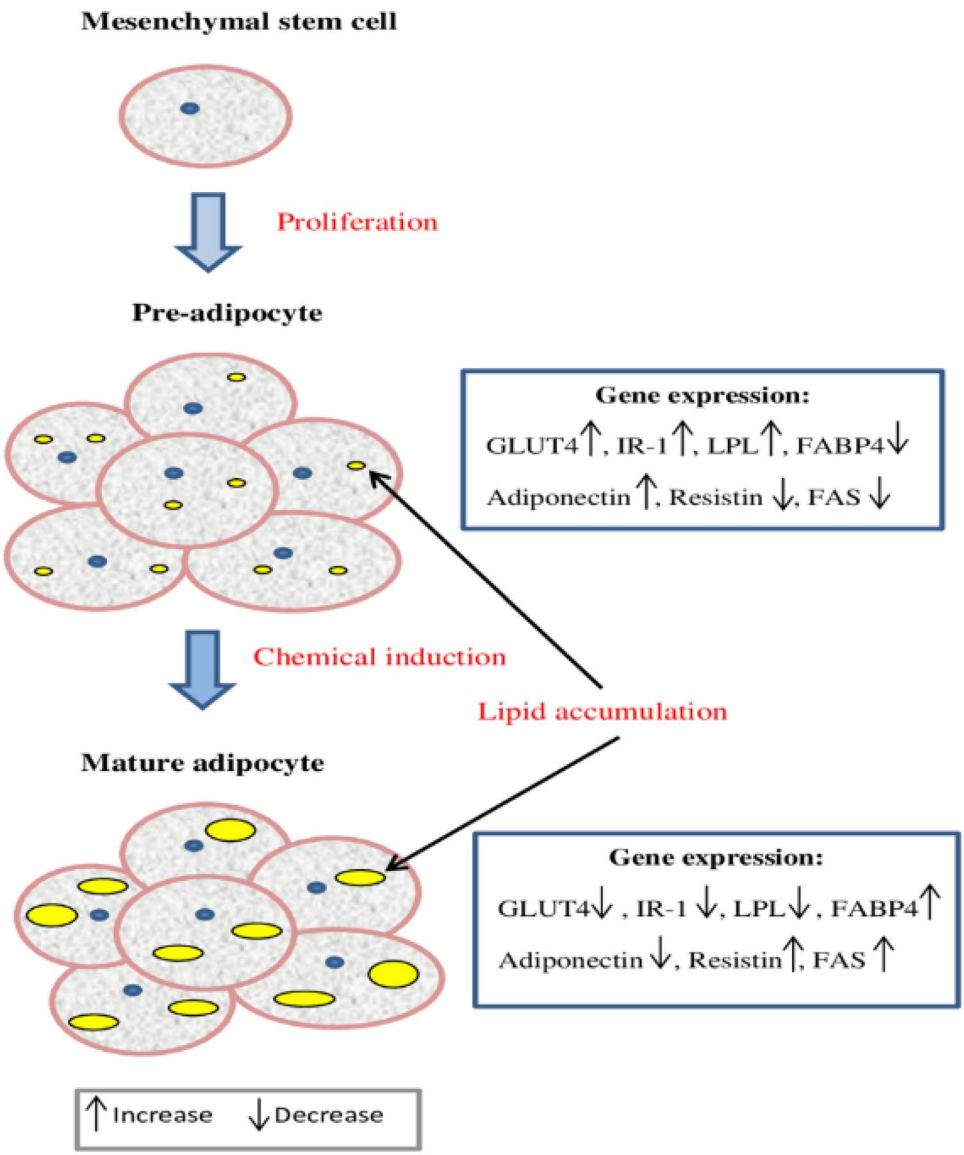

Fig. 1 Mouse embryonic stem cells induced chemically to attain adipocyte like cells. When the adipocyte characteristic occurs in the 3T3-L1 cell line, the functionally important specific protein (IR-1, Adiponectin, GLUT4, and LPL) decreases (↓) and the expression of adipocyte markers (FABP4, Resistin, and FAS) increases (↑)

and drug targeting due to the high degree of morphological and functional differentiation in vitro.

Mechanism of an adipogenesis signaling pathway in 3T3-L1

Adipocyte is a metabolic disease which affects not only the lipid metabolism but also glucose and protein metabolism. Studies have shown that the adipogenic pathogenesis is correlated with various signaling pathways, such as the adenosine monophosphate-activated kinase (AMPK) pathway, insulin signaling pathway, PPAR regulation, and glucose pathway. These signaling pathways have become the main source of promising drug targets for treating obesity and metabolic diseases. These signal pathways involved in 3T3-L1 are discussed below, and the corresponding signal pathways are illustrated in Fig. 2.

Insulin signaling pathway

Insulin resistance is partially mediated by lowering the expression level of the insulin receptor (IR). This is followed by subsequent tyrosine phosphorylation of IRS1, impaired tyrosine phosphorylation of IR, and subsequent deactivation of its catalytic subunit. Therefore, the reduction of glucose transport and the serine/threonine protein kinase B (Akt) activated when there is a reduction in the Phosphatidylinositol 3-kinase (PI3K) signaling pathway. Adipocyte differentiation was facilitated by the activation of several kinases, particularly PI3K kinases, thus activating p38 mitogen-activated protein kinases (MAPKs), resulting in adipocyte synthesis. Pro-inflammatory molecules such as IL-6, TNFα,

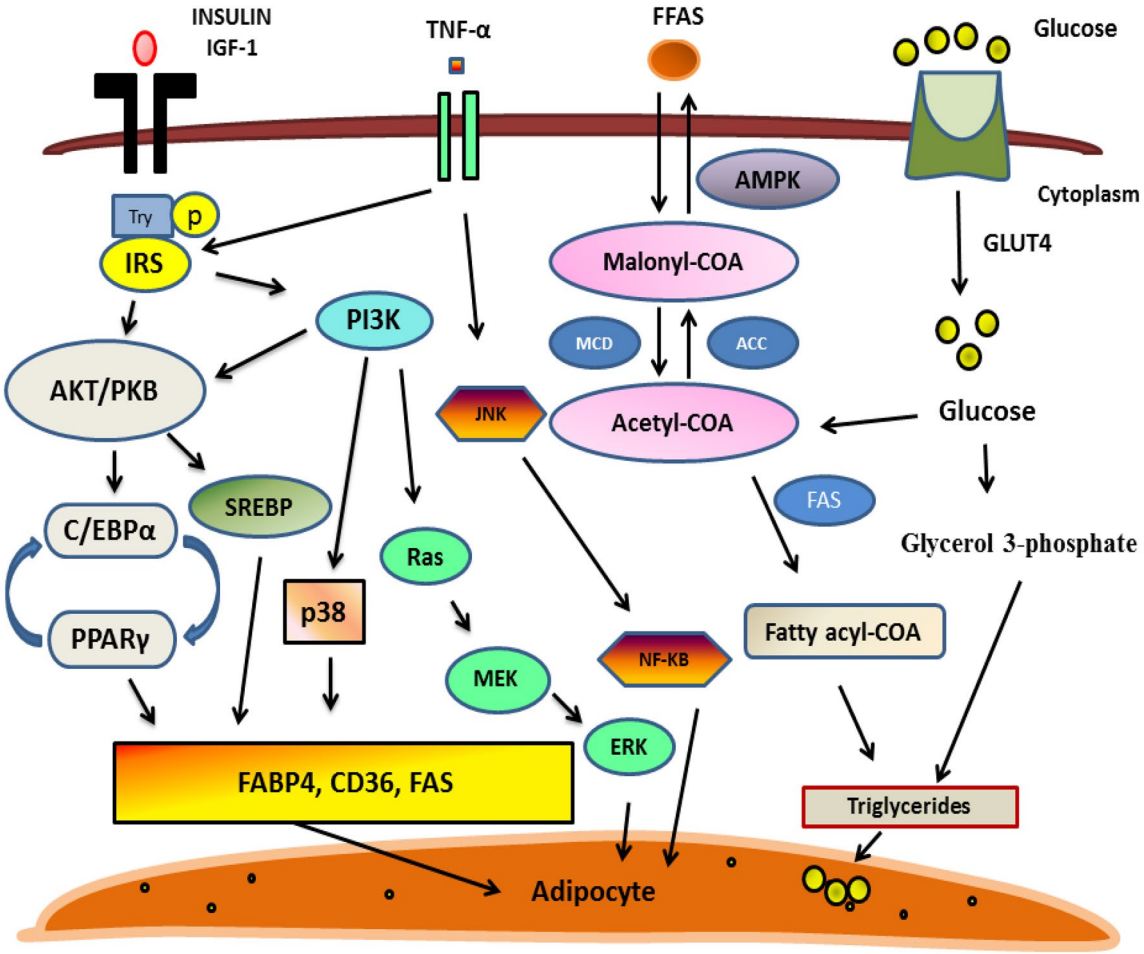

Fig. 2 Adipogenesis signaling pathway. The cascade of insulin signaling is divided into two main pathways. The Akt and PI3K pathway, both support insulin action on nutrient metabolism including glucose absorption. IR activation leads to IRS1 tyrosine phosphorylation, thereby initiating signal transduction. NF-KB inflammatory pathways activation reduces the signaling ability of IRS1. Dephosphorylation of AMPK activates the acetyl coenzyme A (acetyl CoA) and it decreases glucose uptake which leads to triglycerides synthesis

and Monocyte chemoattractant protein-1 (MCP-1) in adipose tissue affect the insulin signaling independent IRS1 and enhanced inflammatory signaling pathway activation such as c-Jun N-terminal kinase (JNK) and nuclear factor kappa light chain enhancer of activated B cells (NF-KB) in the tissue. Insulin signaling activates intracellular signaling cascades in the PI3K and extracellular signal regulated kinase (ERK) pathways. Thus, this defective insulin signaling pathway contributes to adipogenesis in 3T3-L1 [10].

PPAR regulation

Akt has been suggested for multi-level regulation of SREBP1 nuclear translocation. Akt promotes the transport of SREBP1 by endoplasmic reticulum to golgi via direct phosphorylation of SREBP and facilitates the interaction of SREBP1 with protein-complex II vesicles. Therefore, Akt is a positive regulator for the translocation of SREBP1, and SREBP family transcription factors can control PPARγ expression, thus inducing lipogenesis [11].

C/EBPβ is expressed at the early stage of differentiation and stimulates C/EBPα and PPARγ transcription. The expression of lipid metabolizing enzymes such as FABP4, lipoprotein lipase (LPL), and FAS is regulated during adipogenesis by PPARγ and C/EBPα. CD36 was positively correlated with PPARγ, indicating that reduced PPARγ expression associated with the silencing of the CD36 gene may result in impaired adipocyte differentiation. This is consistent with the findings that PPARγ downregulation impairs preadipocyte differentiation. Simultaneously, its upregulation is correlated with CD36 upregulation and increased differentiation [12] so that the chemical induction in 3T3-L1 increased PPARγ expression, leading to adipocyte differentiation.

AMPK pathway

AMPK act as a central regulator of energy sensor and energy homeostasis. It increases glucose uptake by inducing GLUT4. Activated AMPK disables gluconeogenic enzymes, thus reduces the production of hepatic glucose. AMPK activates malonyl-CoA decarboxylase and stimulates lipid metabolism by inhibiting ACC, where malonyl CoA acts as the fatty acid synthesis chain elongating component. Therefore, malonyl CoA is regulating the equilibrium between the synthesis of fat and oxidation of fat. The concentration of cellular malonyl CoA was regulated by two enzymes, ACC and malonyl CoA decarboxylase. Moreover, the cellular malonyl CoA helps in converting acetyl CoA to malonyl CoA and then back to acetyl CoA [13]. Where excess acetyl CoA formation from dietary sources leads to increases in ACC and ACC mediated malonyl-CoA production, simultaneous increases in fatty acid synthesis and decreases in fatty acid oxidation result in net energy storage as triglycerides.

Glucose pathway

Excess ingestion of carbohydrates is a major cause of obesity. Triglycerides are the dominant lipid in adipose tissue. This contains a backbone of glycerol and free fatty acids. Glucose is the leading carbohydrates representative. The glucose metabolism provides all the substances which are required for triglyceride synthesis. Glycerol is formed by glycolysis. By the action of glycerol-3-phosphate dehydrogenase, dihydroxyacetone-P is converted to glycerol-3-phosphate; also, glycerol is used in triglyceride synthesis. Insulin was released by excess plasma glucose load and activated ACC. Insulin also facilitates the absorption of glucose by GLUT4 receptors, thereby supplying precursors for fatty acid synthesis and activating LPL. This offers more fatty acids that are produced by lipoprotein degradation for glycerol esterification. Fructose in the liver undergoes faster glycolysis than glucose because it bypasses the regulatory step that phosphofructokinase catalyzes. Excess production of pyruvate by fructose consumption is leading to the development of intermediate Krebs cycles. Accumulated citrate can be transported from the mitochondria to the hepatocyte cytosol, converted lyase to acetyl CoA, and synthesized with fatty acids. As previously mentioned, dihydroxyacetone phosphate can be converted to glycerol-3-phosphate, supplying the triglyceride molecules with the glycerol backbone. Triglycerides are processed into very-low-density lipoprotein (VLDL), released from the liver to process both fat and muscle cells towards the peripheral tissue [14, 15]. The triglycerides are produced in mature adipocytes when the 3T3-L1 cells are differentiated via the same adipogenesis pathway.

Warning effect of the existing drugs and need for other therapies

Existing drugs like Sibutramine, Orlistat, Lorcaserin, Naltrexone, and Liraglutide have been reported that they are successfully controlling obesity (Fig. 3). However, the cessation they provide is not stable; moreover, they can also lead to severe side effects.

For instance, Sibutramine has been involved with a slight elevation on pulse rate, blood pressure, and inhibition of human Ether-a-go-go-Related Gene (hERG), resulting in possible cardiovascular toxic effects with pre-existing cardiovascular disease and hypertension, hence this medicine is not recommended. In a few cases, Orlistat was associated with severe hepatic adverse events such as acute cholestatic hepatitis and subacute hepatic failure. It has a weak Cytochrome P450 3A4 inducer and a Pregnane x receptor activator. Orlistat inhibits pancreatic and gastric lipase, leading to unpleasant side effects of the gastrointestinal tract, including cramping of the abdomen and stomach flatulence [16]. Lorcaserin should not be co-administrated with other drugs when there is a potential risk of serotonin syndrome, which results from excessive stimulation of 5-hydroxytryptamine receptor 2A. Caution should be exercised because it can affect the serotonergic neurotransmitter pathway. Naltrexone drug caused severe headache, anxiety, and hallucinations that had been resolved when the drug has been discontinued from individuals. Nausea and gastrointestinal disorders have been reported more frequently with liraglutide [17]. Therefore, to treat this chronic disease, there is an important need to look for new, safer, and potent medicine. Natural bioactive compounds are an excellent alternative method for creating efficient, healthy, and cost-effective anti-adipogenesis agents. Dietary plant-derived bioactive compounds may be used as anti-obesity agents because they can suppress adipose tissue development, inhibit preadipocyte differentiation, promote lipolysis, and induce apoptosis of existing adipocytes, thus reducing the mass of adipose tissue. The anti-adipogenic effects of the different bioactive compounds are listed in Table 1 with information about their effects and molecular mechanism in 3T3-L1.

Natural bioactive compound and their anti-adipogenic property in 3T3-L1 cell line

Alkaloid

Alkaloids are naturally present in plants, especially in floral plants that contain carbon, hydrogen, nitrogen, and usually oxygen. A single plant species usually consists of few

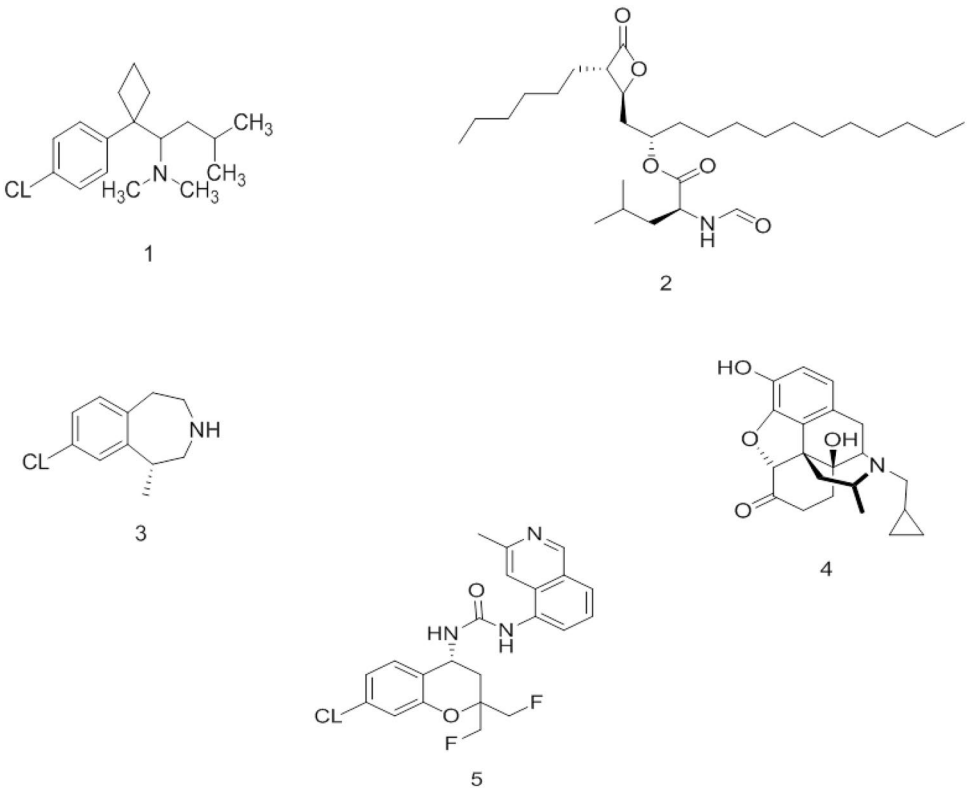

Fig. 3 Chemical structure (Courtesy: ChemDraw® JS) of approved anti-obesity drugs: Sibutramine (1), Orlistat (2), Lorcaserin (3), Naltrexone (4) and Liraglutide (5). Due to potential side effects and limited evidence of small weight loss benefits, particularly in adolescents, most of these anti-obesity medications are not recommended

alkaloids, but several plant families, including Solanaceae, Papaveraceae, Ranunculaceae, and Amaryllidaceae, are mostly rich in several alkaloids forms. In the majority, only four groups of alkaloids (Fig. 4) have the potential to anti-adipogenesis activity, i.e., indole, isoquinoline, amino, and terpenoid alkaloids [91].

Berberine

Berberine was isolated from various plants, including *Berberis vulgaris*, *Tinospora cordifolia*, *Hydrastis canadensis*, and *C. chinensis*. It enhances the activity of insulin by activating the AMPK helps to regulate the cellular uptake of glucose, oxidation of fatty acids, and increases glucose activity in 3T3L-1. Another potential character of this berberine in 3T3-L1 is reducing insulin resistance [92].

Palmatine

Palmatine was a naturally occurring isoquinoline alkaloid found in traditional Chinese medicines, isolated from *Tinspora sagittata*. The effectiveness of palmatine in the regulation of hyperlipidemic and hyperglycemic conditions has been reported. It substantially inhibited the differentiation of adipocytes by reducing many adipocyte-specific transcription factors, including PPARγ and C/EBPα through inhibition of Rapidly accelerated fibrosarcoma (Raf)/Mitogen-activated protein kinase (MAPK)/Extracellular signal-regulated kinase (ERK) pathway phosphorylation in 3T3-L1 preadipocytes [93].

Coptisine

Coptisine alkaloids isolated from *Dicranostigma leptopodum*, and while screening, it was found to inhibit lipid content significantly, and the isolated alkaloids may have a therapeutic interest in obesity therapy. During adipocyte differentiation, the 3T3-L1 cells were fully differentiated with the expression of PPARγ and C/EBPα, but when coptisine was treated, it strongly inhibited the accumulation of cellular triglycerides in 3T3-L1 adipocytes; also, coptisine mediated the inhibition of major adipogenic factors such as PPARγ and C/EBPα in 3T3-L1 [50].

Piperine

Piper nigrum (Black pepper), of the piperaceae family, is one of the most widely used condiments globally. Piperine was the primary alkaloid of black pepper. It was shown to activate protein kinase and PPARγ in high-fat diet-induced obese mice and attenuate high fat-induced obesity. Piperine also plays a key role in lowering blood glucose and lipid levels. It decreases the differentiation of fat cells by reducing PPARγ activity and suppressing the expression of SREBP-1

Table 1 Phytochemical compounds of various medicinal plants, their metabolic and cellular efficiency dose on 3T3-L1 cells in vitro

Bioactive compound	Plant source	Metabolic and cellular efficacy	References
Mahanimbine	*Murraya koenigii*	Enhance the glucose uptake at 1 mM concentrations	[18]
Boldine	*Peumus boldus*	Increase adiponectin secretion in 3T3-L1 adipocytes at 5–25 μM	[19]
Trigonelline	*Trigonella foenum graecum*	At 100 μM significantly reduce gene expression of PPARγ mediated adipogenesis pathway	[20]
Arecoline	*Areca catechu*	GLUT4 and IRS2 gene expression substantially increased via PPAR pathway at 25 μM	[21]
Berberine	*Berberis*	In addition of 8 μM decreased adipogenesis induction with down-regulated mRNA and protein expression levels of SREBP-1 related protein	[22]
Theobromine	*Theobroma cacao*	Inhibit adipocyte differentiation in the early stages of adipogenesis by controlling the expression of PPARγ and C/EBPα in 3T3-L1 preadipocytes via AMPK and ERK/JNK signaling pathways at 150 μg/ml	[23]
Genistein	*Genista tinctoria*	Inhibit adipogenesis process at 100 μM and on lipid metabolism of mature adipocytes	[24]
Apigenin	*Citrus depressa*	Activation of AMPK results in reduced lipolytic and adipogenic gene expression, thereby suppressing adipogenesis in 3T3-L1 at 50 μM	[25]
Catechin	*Camellia sinensis*	Improves adiponectin expression and enhances the uptake of glucose in 3T3-L1 adipocytes at 50 μM	[26]
Kaempferol	*Kaempferia galanga*	Delayed progression of the cell cycle from the S to G2/M phase by dose-dependent manner from 10 to 50 μM concentration	[27]
Myricetin	*Abelmoschus moschatus*	Significant decrease in triglyceride intracellular accumulation based on the dose concentration from 0.001 to 1 μmol/L	[28]
Nobiletin	*Citrus reticulate*	Improved adipocyte differentiation and lipolysis through triggering cAMP-mediated signaling cascades in 3T3-L1 adipocytes at 100 μM	[29]
Quercetin	*Vitis vinifera*	Decreased triglyceride at 10 mM	[30]
Rutin	*Phyllanthus amarus*	Adipogenic transcription factor such as PPARγ and C/EBPα in 3T3-L1 cells remarkably down-regulated at 1 mg/ml concentration	[31]
Limonene	*Citrus reticulate*	Induce glucose absorption at 10 μM by triggering the signaling pathways p38MAPK and Akt	[32]
Gallic acid	*Terminalia chebula*	When treated with 100 μM induces apoptosis via FAS and the mitochondrial system in 3T3-L1 pre-adipocytes. Gallicacid induction of cell apoptosis can be a key mechanism for decreasing pre-adipocyte proliferation	[33]
Tannic acid	*Terminalia chebula*	Reduced FAS expression and downregulated PPARγ mRNA levels during the adipocyte differentiation of 3T3-L1 cells at 2.5 and 5 μM concentration	[34]
β-carotene	*Daucus carota*	30 μM concentration in 3T3-L1 enhanced gene expression to insulin sensitivity, including adiponectin, GLUT4 and lipid binding adipocyte antigen	[35]
Anthocyanin	*Glycine max*	Significant repression of the target gene and protein expression of such lipogenic transcription factors as stearyl-CoA desaturase, ACCα and FAS at 40 μg/ml concentration	[36]

Table 1 (continued)

Bioactive compound	Plant source	Metabolic and cellular efficacy	References
Esculetin	*Vaccinium myrtillus*	AMPK activation in 3T3-L1 cells at 100 μM exhibit reduced lipid aggregation and blocked the expression of ap2	[37]
Chicoric acid	*Echinacea purpurea*	Downregulate HO-1 and COX-2 via PI3K/Akt pathway when treated with increasing concentration from 10 to 200 μM	[38]
Scopoletin	*Scopolia carniolica*	Significantly increased the LPL activity in 3T3-L1 adipocyte in dose-dependent manner from and maximum activity was observed at 10 μg/ml	[39]
Ursolic acid	*Crataegus pinnatifida*	Concentration ranging from 2.5 to 10 mM attenuated adipogenesis with reduced protein expression of PPARγ, SREBP1 and C/EBPα	[40]
Indole-3-carbinol	*Brassica oleracea*	Reduced mRNA level of adipogenic genes that encode for PPARγ and adipocyte protein 2 in 3T3-L1 cells at 100 μM	[41]
Quercetin	*Lagerstroemia speciosa*	A dose of 10 μM tended to decrease PPAR gene expression and diminished triglycerides accumulation	[42]
Apigetrin	*Teucrium gnaphalodes*	The mRNA level of adipogenic transcription factor genes such as FAS, SREBP-1, and C/EBP suppressed after treatment at 100 μM	[43]
Quercetin, hibifolin, gossypetin & hyperoside	*Abelmoschus manihot*	Triglyceride accumulation is inhibited and the apoptosis of mature adipocyte at 30 mM, thereby suppressing the differentiation	[44]
Asarone	*Acorus calamus*	Asarone compound (62.5 and 125 μM) from *Acorus calamus* rhizome induce lipolysis stimulation by increasing the activity of hormone-sensitive lipase	[45]
Feruloylquercitrin	*Albizia julibrissin*	Treated with 30 μM, it reduced cellular FAS gene, then glyceraldehyde 3 phosphate dehydrogenase (GPDH) and triglyceride level diminished	[46]
Hispidin	*Alpinia zerumbet*	Increase the intracellular CAMP and glycerol 3 phosphate inhibited at 250 μg/ml	[47]
Cirsiliol & jaceosidin	*Artemisia scoparia*	At 20 μM, it inhibited the accumulation of triglycerides in 3T3-L1 preadipocytes	[34]
Cinnamyl alcohol	*Castanea crenata*	Inhibits the formation of fat from carbohydrates by reducing the expression of the FAS gene at 5 and 10 μg/ml	[48]
Kaempferol	*Cinnamomum osmophloeum*	At 20 μM induces adiponectin secretion and activation of GLUT4 to phosphorylate insulin receptor-β and PI3K	[49]
Berberine	*Coptis chinensis*	Significantly reduce gene expression of C/EBPα and PPARγ over a range of concentration (12.5–50 μM)	[50]
Cyclocarioside	*Cyclocarya paliurus*	Activate AMPK-MAPK pathway and prevent proliferation of 3T3-L1 at 10 μM	[51]
Luteolin & coumarin	*Euphorbia lunulata*	At 30 μM, it shows activity by no production of lipopolysaccharide and interferon-γ to activate macrophages in 3T3-L1 for adipogenesis	[52]
Lanostane	*Ganoderma lucidum*	Treated in 3T3-L1cell line, GPDH activity is suppressed significantly at 80 μM by 72% in the cells	[53]
α-mangostin	*Garcinia malaccensis*	Release of free fatty acid to medium in 3T3-L1 at 50 μM due to the expression of leptin	[54]

Table 1 (continued)

Bioactive compound	Plant source	Metabolic and cellular efficacy	References
Anthocyanin	*Glycine max*	Regulates lipolysis in the adipocyte and has the lowest cytotoxic and cholesterol activity at 50 μg/ml	[55]
Idescarpin	*Idesia polycarpa*	Regulation of lipogenesis by the anti-adipogenic property at 50 μM in 3T3-L1	[56]
Caffeic acid, rutin, ursolic acid & chlorogenic acid	*Ilex paraguariensis*	Inhibits the gene expression related to adipogenesis leptin, C/EBPα, TNF-α and PPARγ at 50 μg/ml in 3T3-L1	[57]
Ellagitannin	*Lagerstroemia speciosa*	Influences the cell cycle and acquisition of lipid, then translocation via Akt/IRS1/PI3K pathway and p38, JNK and ERK phosphorylation were inhibited; later activity of anti-obesity and glucose uptake has been stimulated to have the ability to suppress adipocyte at 0.5 mg/ml concentration	[58]
Benzophenone C-glucosides	*Mangifera indica*	Increase the AMPK enzyme and downregulated in expression of FAS based on the 30 μM dosage the lipid storage prevented and minimizes SREBF1, C/EBPα and PPARγ expression	[59]
Licarin B	*Myristica fragrans*	Improved insulin sensitivity and enhanced adiponectin secretion at various doses (5, 10, and 15 μM)	[60]
Isoquercitrin	*Persicaria hydropiper*	Increase the Wnt/β-catenin activity at 50 μM in 3T3-L1	[61]
Vitexin & orientin	*Spirodela polyrhiza*	Declining level of C/EBP and PPAR after exposure at various concentrations 40, 100 and 200 μg/ml	[62]
Myricetin-3-O-rhamnoside & europetin-3-O-rhamnoside	*Syzygium aqueum*	Increase adiponectin secretion in 3T3-L1 adipocytes and increased glucose uptake at 0.08–10 μM	[63]
Saikosaponij	*Bupleurum falcatum*	NF-KB inhibited through the ERK pathway at 100 nM	[64]
Fucoidan	*Undaria pinnatifida*	Adipocyte protein 2 and expression of inflammation-related genes substantially suppressed during adipogenesis in 3T3-L1 adipocytes at 100 μg/ml	[65]
Chlorophyll a	*Ludwigia octavalvis*	At concentration 5–30 nM, it exhibited an upregulation of AMPK and arrest cell cycle	[66]
6,6′-bieckol	*Eisenia bicyclis*	Significantly reduced FAS and ACC at a concentration of 10, 25, and 50 μg/ml	[67]
Indole-2-carboxaldehyde & indole-6-carboxaldehyde	*Sargassum thunbergii*	Inhibited lipid accumulation and activation of the AMPK signal pathway at 100 μM	[68]
Caffeine	*Coffea*	Inhibits adipogenesis in 3T3-L1 adipocytes by modulating clonal mitotic expansion and Akt/glycogen synthase kinase 3 (GSK3) pathway at 5 mM	[69]
Cycloastragenol	*Radix astragali*	Dose-dependent decreased cytoplasmic lipid droplet with the IC50 value of 13 μM in 3T3-L1 adipocyte	[70]
Aporphine	*Nelumbo nucifera*	Treated in 3T3-L1 cell, AMPK mediate the glucose consumption at 0.5–50 μg/ml	[71]
Friedelin	*Garcinia prainiana*	Significant in stimulating glucose uptake at 10 μM	[72]
6-hydroxydaidzein	*Glycine max*	Improving sensitivity at 20 μM concentration	[73]
Chebulagic acid	*Terminalia chebula*	Increases the glucose transport and increased levels of adiponectin at 100 μM	[74]

Table 1 (continued)

Bioactive compound	Plant source	Metabolic and cellular efficacy	References
Oleanolic acid	*Phytolacca americana*	PPARγ activation significantly blocked at 25 μmol/L	[75]
Loganic acid	*Gentiana lutea*	Key adipogenesis related genes such as adiponectin, TNF-α and LPL significantly reduced after treatment at 50 μg/ml	[76]
6-shogaol	*Zingiber officinale*	Inhibited the development of two major adipogenesis regulators, PPARγ and C/EBPα as well as induced lipolysis in mature adipocyte 3T3-L1 at 40 μM	[77]
Nonivamide	*Capsicum oleoresin*	At 15–100 μM reduce lipid accumulation	[78]
Aspalathin	*Green rooibos*	At the protein level, the IRS1 and AMPK phosphorylation and GLUT4 expression increased, while decreased serine/threonine kinase Akt activation at 10 μM concentration	[79]
Fisetin	*Fragaria ananassa*	Promote the gene expression of adiponectin at 1 μM concentration	[80]
Carnosic acid	*Rosmarinus officinalis*	Inhibition of clonal mitotic expansion and may not interfere with rated of C/EBP mRNA level, however, it prevented the expansion of PPARγ and FABP4 at 7.5 μg/ml	[81]
Daidzein	*Glycine max*	Downregulated the expression of LPL, SCD-1, ACC, and FAS at a various concentration (10, 50, 100, and 200 μM)	[82]
Bouchardatine	*Bouchardatia neurococca*	SCD-1, FAS, and ACC protein levels were subsequently reduced at 50 μM	[83]
β-asarone	*Acorus calamus*	Treatment at 0.25 mM reduced the phosphorylation of ERK1/2	[84]
Hirsutenone	*Alnus glutinosa*	At 80 μM adipogenesis was attenuated by directly targeting PI3K and ERK specifically	[85]
Lignan	*Knema patentinervia*	Significantly improved glucose uptake in a dose-dependent manner from 10, 20 and 50 μg/ml	[86]
Hispidulin	*Salvia plebeia*	Control obesity by regulating PPARγ at 40 μM	[87]
Stevioside	*Stevia rebaudiana*	Direct effects on insulin sensitivity of 3T3-L1 by increased glucose absorption at 60 and 90 μM	[88]
Osthole	*Cnidium monnieri*	Inhibited NF-KB translocation and suppressed phosphorylation of MAPK at 100 μM in 3T3-L1 adipocyte	[89]
6-paradol	*Zingiber officinale*	Stimulating glucose utilization and AMPK phosphorylation in 3T3-L1 adipocyte at 100 μM concentration	[77]
β-taraxerol	*Mangifera indica*	PI3K dependent PKB activation accompanied by sequential inactivation of GSK3β phosphorylation at 100 ng/ml	[90]

and C/EBPα in the 3T3-L1 cell line, contributing to the potential treatment of obesity-related disease [94].

Theobromine

Theobromine, a caffeine derivative found primarily in cocoa beans and dark chocolate, is part of a family of alkaloid molecules known as methylxanthines associated with caffeine and theophylline. The toxicity of theobromine in humans was very low. Theobromine reduces leptin, and Adipocyte protein 2 (Ap2) messenger ribonucleic acid (mRNA) expression prevents the formation of lipid droplets. Theobromine treatment in the 3T3-L1 cell line prevents adipocyte differentiation in the early stages of adipogenesis by controlling the expression of PPAR and C/EBPα through the signaling pathways of AMPK and ERK/JNK [23].

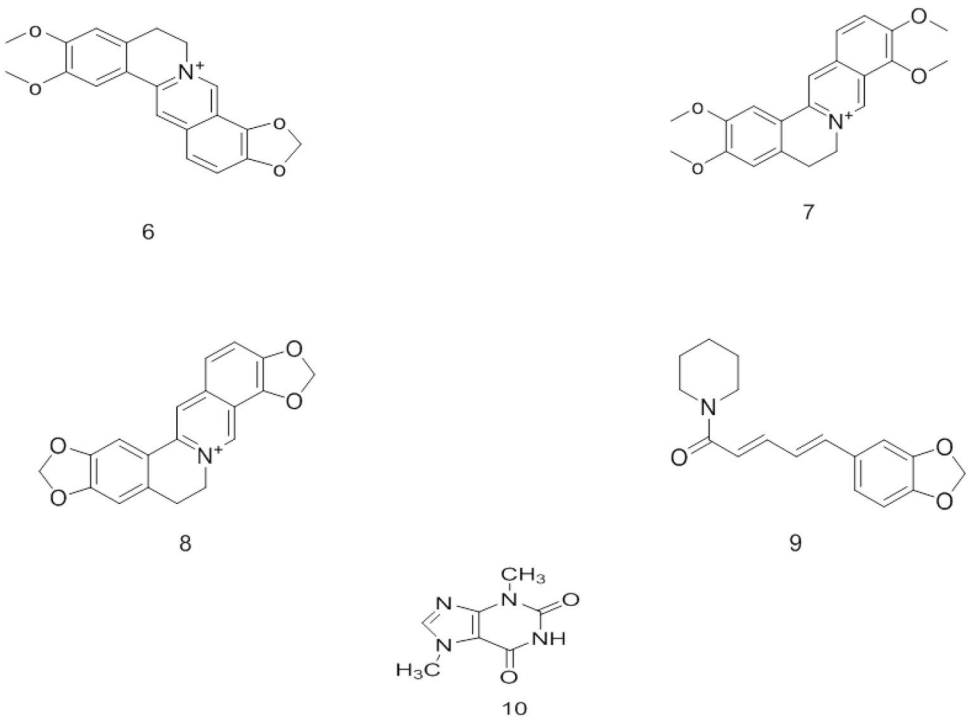

Fig. 4 Chemical structure (Courtesy: ChemDraw® JS) of alkaloid investigated as antiadipogenic agents: Epiberberine (6), Palmatine (7), Coptisine (8), Piperine (9) and Theobromine (10)

Flavonoid

Flavonoids are widely distributed secondary metabolites in plants and are synthesized via phenylpropanoid pathways. They are identified by the C-ring's degree of oxidation and include flavonols, anthocyanins, and flavan-3-ols. These molecules (Fig. 5) may undergo changes in their aromatic cycles, including glycosylations, hydroxylations, methylations, and acylation, making the diversity of a compound class. The plants rich in flavonoids are *B. oleracea*, *Lactuca sativa*, *Phoenix dactylifera*, and *Solanum lycopersicum*. Flavonoids have been known to increase insulin secretion,

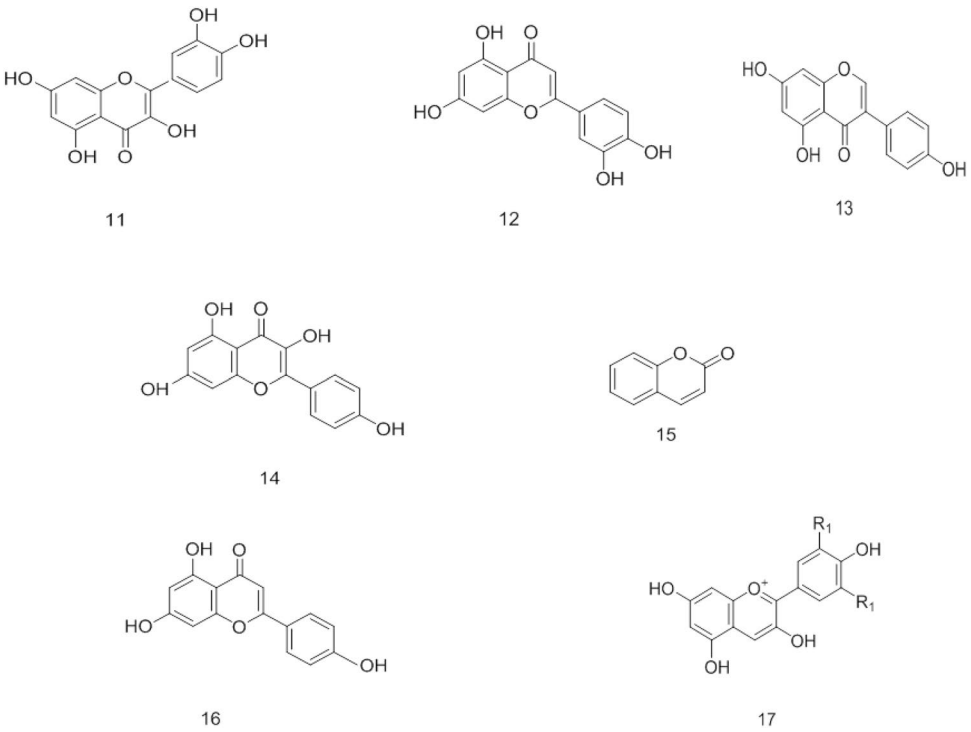

Fig. 5 Chemical structure (Courtesy: ChemDraw® JS) of flavonoids investigated as antiadipogenic agents: Quercetin (11), Luteolin (12), Genistein (13), Kaempferol (14), Coumarin (15), Apigenin (16) and Anthocyanin (17)

stimulate pancreatic β-cell proliferation, consume glucose, minimize insulin resistance, inflammation, and oxidative stress [95].

Quercetin

Quercetin was an effective hydroxyl antioxidant, and the presence of metal ions influences the biological activities of quercetin. *Tridax procumbens*, *Aesculus indica*, and *Rubus fruticosus* are some of the plants from which quercetin is isolated. It is the most potent scavenger of reactive oxygen species in the flavonoid family. These properties make quercetin a good inhibitor of lipid peroxidation. In 3T3-L1, by activating the AMPK pathway, quercetin may exercise its anti-adipogenesis activity, while quercetin induced apoptosis of mature adipocytes appears to be mediated through ERK and JNK pathway that play critical roles in apoptosis. In particular, quercetin supplementation in mice significantly reduced obesity caused by a high-fat, decreasing body, liver, and white adipose tissue weight [96].

Luteolin

Luteolin, a tetrahydroxyflavonea group of naturally occurring compounds that are commonly found in the plant kingdom. It has potent antioxidant and anti-inflammatory properties. Treatment with luteolin reduced TNFα, MCP-1, and IL-6 mRNA levels and enhanced AKT phosphorylation. By inhibiting adipocyte differentiation, such as triglycerides accumulation, luteolin had an anti-obesity effect rather than stimulating the energy consumed by lipid oxidation. To prevent obesity and promote good health, it is advised to consume luteolin rich foods such as chamomile tea. As a nutraceutical anti-obesity compound, luteolin could also be a candidate compound [97].

Genistein

Genistein, a soy-derived isoflavone, has been identified as having therapeutic effects on diabetes and obesity. Genistein blocked the tyrosine phosphorylation of C/EBP. It inhibited the proliferation of 3T3-L1 cells through apoptosis activation and the pathway associated with estrogen receptor α, thereby inhibiting adipogenesis and induced lipolysis [98].

Kaempferol

Natural flavonoid kaempferol was a polyphenolic compound found in berries, vegetables, green tea, black tea, and several medicinal plants such as pumpkin and carrot. In vivo and in vitro studies have shown that kaempferol has beneficial roles in inflammation, hyperglycemia, hyperlipidemia, and diabetes. Kaempferol postponed the S to G2/M process and affected adipocyte proliferation by inhibiting the cell cycle's progression during the S phase. Thus kaempferol prevents lipid accumulation through lipid metabolism-related genes and cell cycle control during 3T3-L1 adipocyte differentiation [27].

Coumarin

Coumarin compounds include a very large class of plant-based phenolic substances. These are present at high levels in some essential oils, including cinnamon bark oil; they are also found in green tea, chicory, and fruits such as bilberry [37]. Isolated coumarin from *Fraxinus rhynchophylla* prevents adipocyte differentiation in 3T3-L1 cells by reducing fat accumulation through PPARγ dependent pathway inhibition [99].

Apigenin

Apigenin [5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one] was a naturally occurring plant flavone abundant in certain fruits and vegetables, and it was also a bioactive flavonoid with anti-inflammatory and antioxidant properties. At the same time, obesity was associated with increased oxidative stress and inflammation in adipose tissue, which mediates the beneficial role of apigenin in adipose tissue development. Apigenin isolated from the *Daphne genkwa* prevents the separation of 3T3-L1 preadipocytes by preventing clonal expansion and impairing the DNA binding operation of C/EBP [100].

Anthocyanin

A wide range of biological activities in mice and streptozotocin-induced diabetic rats have been documented in anthocyanin studies, including antioxidant and anti-hyperglycemic behavior [36]. Anthocyanin found rich in *Citrus sinensis* is effectively inhibits weight gain and insulin resistance by suppressing GPDH, PPARγ expression, and reduces the lipid accumulation in 3T3-L1 adipocyte differentiation [55].

Phenol

Phenolic compounds are secondary metabolites formed by phenylpropanoid metabolization in the shikimic acid of plant and pentose phosphate. This includes benzene rings with one or more hydroxyl equivalents, ranging from simple phenolic clusters to highly polymerized compounds.

Dietary polyphenols also influence peripheral glucose absorbed in insulin-sensitive tissue. For example, polyphenol elements of berries suppress α-amylase and α-glucosidase enzymes, resulting in lower blood glucose levels following high carbohydrate meals. Phenolic phytochemicals (Fig. 6)

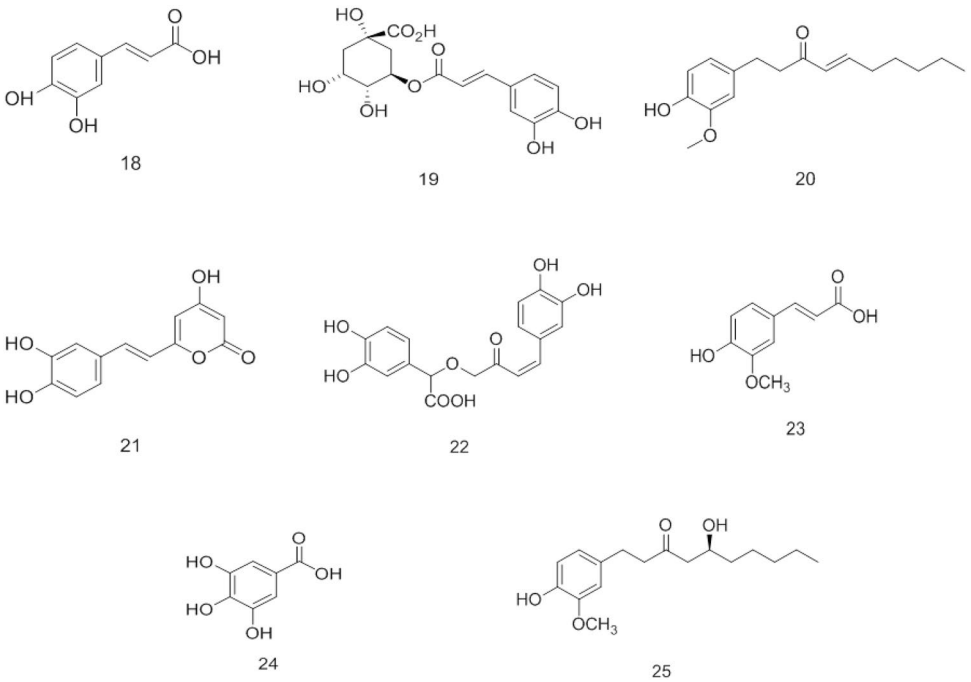

Fig. 6 Chemical structure (Courtesy: ChemDraw® JS) of phenol investigated as anti-adipogenic agents: Caffeic acid (18), Chlorogenic acid (19), Shogaol (20), Hispidin (21), Rosmarinic acid (22), Ferulic acid (23), Gallic acid (24) and Gingerol (25)

have also been shown to control oxidative stress-related chronic diseases such as obesity and diabetes [101].

Caffeic acid

Caffeic acid phenethyl ester was a bioactive compound originally isolated from propolis hives and was known to have anti-mitogen and anti-inflammatory properties. It has an anti-adipogenic effect that reduces the expression of resistin, TNFα, and leptin in 3T3-L1. Caffeic acid has enormous potential health benefits in adipose tissue to prevent obesity and related metabolic disorder [102].

Chlorogenic acid

Chlorogenic acids are phenolic compounds formed with quinic acid by esterifying cinnamic acids, such as ferulic, caffeic, and p-coumaric acids. Green coffee was an important source of chlorogenic acid in nature. The use of green coffee extract has shown antihypertensive effects in rats and humans, regulating human glucose metabolism and inhibitory effects on fat accumulation and body weight in mice. Chlorogenic acid stimulates glucose uptake in both insulin-sensitive and insulin-resistant in 3T3-L1 preadipocyte [103].

6-shogaol

Ginger (*Z. officinale*) is a plant rhizome widely used as a spice and herbal medicine. 6-shogaol was the main component extracted from ginger. It blocked the expression of two key adipogenesis regulators, C/EBPα, and induced lipolysis in mature adipocyte 3T3-L. 6-shogaol contained potentiality in stimulating glucose utilization in 3T3-L1 adipocyte due to increased AMPK phosphorylation [77].

Hispidin

Hispidin, 6-(3,4-dihydroxylstyryl)-4-hydroxy-2-pyrone, was a phenolic material derived from the *Phellinus linteus*. It has a defensive function against DNA damage caused by peroxynitrite and radical hydroxyl generation, thus protects pancreatic β-cells against hydrogen peroxide exposure [47]. Hispidin inhibits melanogenesis in cultured 3T3-L1 adipocytes, associated with PAK-1 dependent obesity and reactive oxygen species and nitric oxide production in differentiated adipocyte cells [104].

Rosmarinic acid

Rosmarinic acid was a natural phenol carboxylic acid, a secondary metabolite found in the Lamiaceae family, commonly used as food herbs such as rosemary and lemon. For experimental diabetes and hyperlipidemia, it has a notable efficiency. The ability to inhibit inflammatory processes and scavenge oxygen-free radicals make rosmarinic acid a suitable candidate for enhancing obesity adipose dysfunction. Rosmarinic acid has a multi-factor anti-adipogenic effect by inhibiting the clonal expansion of mitotic agents, modifying the ratio of different C/EBP forms, and blocking adipogenic transcription factors in 3T3-L1 adipocyte [81].

Ferulic acid

Ferulic acid was a phenolic bioactive compound found in fruit, seeds, and cell walls of commelinid plants such as oats and rice. Ferulic acid reduces the aggregation of intracellular lipids in vitro and prevents high fat dietary obesity in vivo. It exhibits decreased SREBP-1 expression levels and increased MAPKs, ERK1/2, and AMPK phosphorylation in 3T3-L1 cells [105].

Gallic acid

Gallic acid (3,4,5-trihydroxy benzoic acid) was a naturally occurring compound in the *Hippophae rhamnoid* plant and its derivatives, which showed significant cytotoxicity to several tumor cells with higher activity than normal cells. It induces apoptosis through the FAS and mitochondrial pathway in pre-adipocytes 3T3-L1, thus reducing pre-adipocyte proliferation. Gallic acid promotes the absorption of glucose by translocating GLUT4 in 3T3-L1 cells [33].

6-gingerol

6-gingerol [(S)-5-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-3-decanone] was an aromatic polyphenol compound of *Zingiber zerumbet* with specific pharmacological activities. Inhibitory effect of 6-gingerol on adipogenesis activates the signaling pathway for Wnt/β-catenin and attenuating the pathway for Akt/GSK3β in 3T3-L1 adipocytes [106].

Terpenoid

Terpenoids are a large group of organic chemicals present in many higher plants, including insects and fungi. Many terpenoids are found, especially in green and flowering plants such as *Tropaeolum majus* and *Clitoria ternatea*. Bioactive terpenoids (Fig. 7) in herbal or dietary plants can modulate ligand-dependent transcription factors, *i.e.*, proliferator-activated peroxisome receptors. Since PPAR are dietary lipid sensors that control energy homeostasis, eating these terpenoids daily have potential efficiency in managing obesity [107].

Cucurbitane

Cucurbitane triterpenoid was isolated from *Momordica charantia*. In the streptozotocin-induced mouse model, Cucurbitane type terpenoids improved insulin sensitivity and glucose homeostasis in 3T3-L1 adipocytes through activating the AMPK-MAPK pathway, which might have

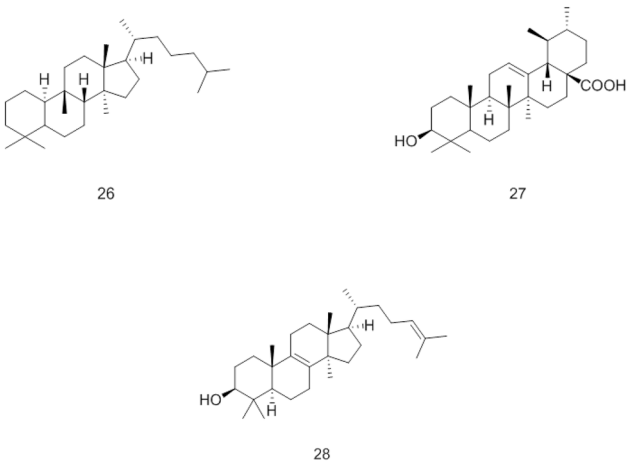

Fig. 7 Chemical structure (Courtesy: ChemDraw® JS) of terpenoid investigated as antiadipogenic agents: Cucurbitane (26), Ursolic acid (27) and Lanosterol (28)

therapeutic potential for insulin resistance and hyperglycemia [51].

Ursolic acid

Ursolic acid is a natural pentacyclic triterpene compound found in the leaves, flowers, and fruits of medicinal herbs such as *Ocimum basilicum*, *R. officinalis*, and *Eriobotrya japonica*. It has many pharmacological functions, including antioxidant, antimutagenic, and anti-hyperlipidemic effects. It inhibited abdominal adiposity in mice, which fed a high-fat diet, thus enhancing lipolysis. Ursolic acid inhibits adipogenesis in 3T3-L1 adipocytes by increased ACC phosphorylation and reduced FABP 4 and FAS protein expression [40].

Lanosterol

Lanosterol was isolated from *G. prainiana* twigs. It may be useful in mimicking the action of insulin that is used to treat patients with type 2 diabetes. In 3T3-L1, lanosterol inhibited adipogenesis by stimulating glucose uptake and maintaining glucose homeostasis [72].

Suggestion and recommendation

It is important to maintain a healthy balance between energy intake and energy expenditure and, thus, between lipid storage and mobilization. Obesity and obesity-related conditions arise when this equilibrium is disrupted and energy consumption exceeds. Adipogenesis inhibition and enhanced lipolysis are the main mechanisms by which these bioactive compounds exert their anti-adipogenesis effects (Fig. 8). Consumers are now aware of their health,

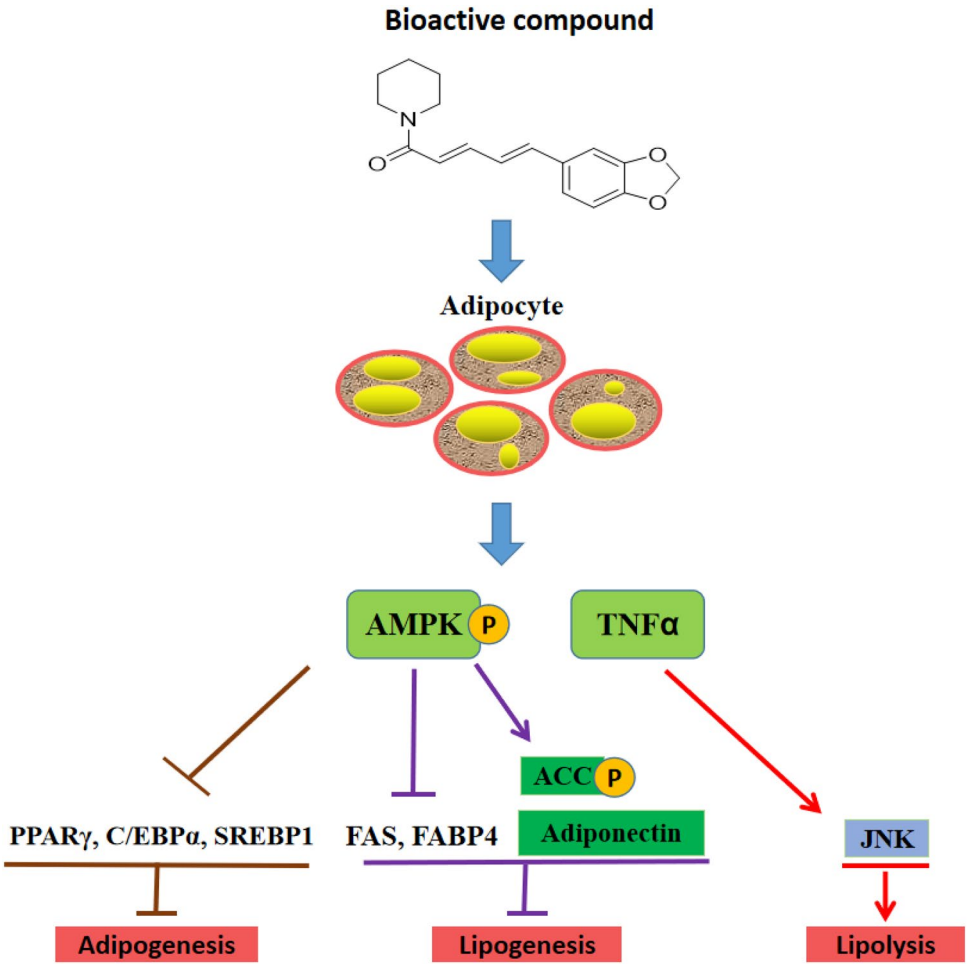

Fig. 8 The mechanism in 3T3-L1 adipocyte against the bioactive compound. The anti-adipogenic activity of the bioactive compound at 3T3-L1 on activation of the AMPK signaling pathway followed by the downregulation of the adipogenic and lipogenic mRNA expression of the related genes (PPARγ, C/EBPα, SREBP1, FAS, and FABP4) and ACC and adiponectin upregulation. TNF-α alpha activates pathways of JNK in adipocytes that are sufficient to induce lipolysis

and in addition to essential nutrition, they now choose foods that have a health-protective effect. One of the main areas for treating obesity is manipulating ingredients utilizing bioactive components in the food industry [108, 109].

- The majority of bioactive compounds such as polyphenols, flavonoids and terpenoids are responsible for the positive well-being effects and are derived primarily from the plant kingdom.
- It is unclear how much of the amount of bioactive compound ingested is absorbed and responsible for the biological effects. Understanding their absorption, metabolism and elimination phases need further work.
- The bioactive components of food are affected by a large number of factors. Therefore, it is important to research the stability of the target compounds in the manufactured products and even during their storage time.
- Therefore, beyond the composition of the normal macronutrients and micronutrients, information on the composition of bioactive compounds in food appears to be important.

Conclusion

Nutrition, physical activity, and drugs often including weight control program. To find new cures with higher efficacy and lower adverse effects, the efficacy of medicinal plants as natural supplements has been into account to reduce body weight. More than sixty bioactive compounds were evaluated in this review about their anti-adipogenic effect and their ability to inhibit the differentiation to adipocyte in the 3T3-L1 cell line. Evolving proof indicates that these compounds may have positive impacts on obesity through a distinct biochemical pathway. To ensure the continued efficacy of weight loss treatment, polytherapy may be needed. These potential plant compounds are either superseded by the existing drug or used combined with the available drugs. Researchers can further explore these plants through their components for their biological activities, as indicated in this review. It can also be examined to use for different secondary disease, and toxicity assay needs to be studied in detail at clinical trials. In general, anti-obesity medicines are preferred based on their high safety and effectiveness. Such exploration will

lead to pharmacological treatment that is safe for human consumption.

Acknowledgements Universiti Putra Malaysia contribution to the research is made possible through research Grant No. LRGS/1/2019/UPM/1.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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