Egypt. J. Chem. **Vol. 66,** No. **SI 13, 763-774** (2023)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

A Review on High Fat Diet-Induced Obesity and Natural Compounds' Role in the Management of Obesity

Sahar Khateeb[a,b*]

[a] *Department of Biochemistry, Faculty of Science, University of Tabuk, 71491, Saudi Arabia*

[b] *Biochemistry Division, Department of Chemistry, Faculty of Science, Fayoum University, Fayoum, Egypt*

Abstract

Obesity is a global problem that causes severe health problems. Since, it increases the risk of developing chronic diseases, such as cardiovascular diseases, cancer, and type 2 diabetes. Pharmacotherapy is still the mainstay for managing obesity, but its efficacy is inadequate, it is non-specific, and it has harmful side effects, so its usefulness is limited. Therefore, it is essential to create new anti-obesity therapy methods or enhance currently available medications, in addition, novel ways could offer insights into obesity and obesity-associated disorders. Natural products, particularly plant extracts, are viewed as an alternative because they have no negative side effects. Plant extracts, in particular, contain antioxidant, anti-inflammatory, and insulin-sensitizing characteristics. Moreover, nanotechnology is one of the promising methods for increasing therapeutic efficacy and improving the anti-obesity effectiveness of these natural chemicals due to their alleged ability to be target-specific. Nanotechnology makes natural chemicals more bioavailable, biodistributable, stable, and soluble. This makes it a promising way to treat obesity.

Keywords: adipose tissue; plant extracts; nanotechnology; obesity.

1. Introduction

Obesity is one of the most serious health issues in the world. It is defined as the accumulation of extra weight that is stored as fat in different parts of the human body [1]. Obesity is thought to be an imbalance between energy intake and expenditure that promotes excessive triglyceride buildup, adipocyte differentiation, and an increase in lipid storage in adipose tissues [2]. It is frequently asserted that dietary fat intake is to blame for the rise in adiposity. Studies on humans have demonstrated that high-fat diets 30% of energy from fat can quickly lead to obesity [3]. The risk of developing obesity is greatly increased by eating too many calorie-dense foods and leading a sedentary lifestyle.

The primary cause of many ailments affecting people nowadays is obesity. It is positively correlated with a shorter life expectancy because it increases a person's risk of developing a wide range of pathological consequences, including coronary heart disease, stroke, liver cirrhosis, type 2 diabetes, several different cancer types, and hypertension [4]. Additionally, over 650 million people worldwide are impacted by obesity. Obesity reduces life expectancy by 5-20 years and is linked to 4.7 million deaths worldwide [5]. Therefore, it is believed that obesity lowers life expectancy and lowers the quality of life.

Environmental or genetic factors can contribute to obesity. The genes that regulate energy homeostasis can become mutated, which leads to genetic obesity [6]. Environmental risk factors for obesity include a high fat intake [7], a high sugar intake [8], a high calorie intake, a lack of physical activity [9], an obesogenic intrauterine environment [10], a lack of sleep [11], endocrine disruptors [12], and a changed gut flora. One of the primary causes of morbidity and mortality worldwide is obesity-related diseases and disorders [13]. Therefore, lowering the obesity incidence is anticipated to minimize obesity-related disorders as well as the risk of morbidity and mortality [14].

Anti-obesity medications are used to treat obesity, but these medications have adverse clinical consequences, such as an increased risk of depression, anxiety, stroke, cancer, and other illnesses, abnormal echocardiograms, and acute kidney injury [15]. Although gastrectomies and liposuction surgeries are effective treatments, they are also intrusive, may have side effects, and even be fatal. So, the critical need for

*Corresponding author e-mail: sms07@fayoum.edu.eg.; (*Sahar Khateeb*).

Receive Date: 04 January 2023, Revise Date: 01 May 2023, Accept Date: 13 May 2023

DOI: 10.21608/EJCHEM.2023.185352.7420

developing innovative preventive treatment modalities targeted at reducing the incidence of obesity is highlighted by the ongoing rise in obesity around the world [16].

Natural products, especially plant extracts, are seen as an alternative because they don't have any side effects. They also make insulin more sensitive, reduce inflammation, and protect cells from damage [17]. Studies have been done on the effectiveness of dietary supplements in lowering obesity. It has been demonstrated that when functional foods are included in a low-energy diet, body mass index, fasting blood glucose, body weight, total cholesterol, waist circumference, LDL-C and triglycerides are reduced in comparison to a low-energy diet alone [18]. The goal of this work is to explain the mechanism by which a high-fat diet leads to obesity and to provide some insights on white adipose tissue and its effect on the development of obesity. Additionally, the potential benefits of using medicinal plants as an alternative treatment for obesity instead of traditional medications were highlighted.

2. Obesity's definition and categories

Obesity is a chronic metabolic condition characterized by a severe accumulation of body fat and a faulty lipid metabolism [19]. Increased calorie consumption and the storage of extra fat in the white adipose tissue depots are the main causes of the epidemic of obesity that affects the entire world [20]. Long-term energy imbalances brought on by excessive energy intake and insufficient energy expenditure have been linked to the emergence of deadly conditions such as cardiovascular illnesses, some types of cancer, and metabolic disorders [21].

The World Health Organization (WHO) defines obesity as an abnormal and excessive fat buildup that can have a negative impact on a human's health. To assess the prevalence of obesity, several indices have been used. Body mass index, known as BMI, is the most widely used indicator [22]. The WHO described how to categorize obesity based on BMI, as seen in Table 1. Adults are considered overweight if their BMI is over 25 kg/m2, and they are considered obese if their BMI is over 30 kg/m2. Severe obesity is defined as having a BMI of 35 kg/m2 or more [23].

The prevalence of obesity is at pandemic proportions worldwide, according to BMI trends [24]. In 2020, the WHO reported that 650 million adults worldwide and 340 million adolescents were obese. In addition, it was found that 38.9 million children under the age of five were overweight [25]. Furthermore, according to data released by the Organization for Economic Cooperation and Development (OECD) in 2019, over 50% of the population in 94% of OECD member states is overweight, and about 25% of them are obese. The OECD predicts that by 2050, diseases related to obesity will kill 92 million people around the world before their time [26].

Table 1: BMI Classification Based on WHO Standards

BMI [Kg/m2]	Category
<18.5	Under weight
18.5–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Class I Obesity
35.0–39.9	Class II Obesity
>40	Class III Obesity

3. Dietary fat intake and obesity

Overeating a high-fat diet is a major contributor to many cases of obesity. Because of the disparity between energy intake and energy expenditure, a high fat diet promotes the development of obesity and metabolic diseases in humans. The feared side effects of a high-fat diet (HFD) include obesity, hypertension, cardiovascular and cerebrovascular disease, type II diabetes, infertility, and even cancer [27]. Also, eating too much dietary fat raises the amount of lipids in adipose and non-adipose tissues, which leads to lipotoxicity and the death of cells [28]. Lipids are essential to a cell's ability to operate normally since they act as an energy source, a signaling molecule, and as lipid bilayers. However, it is now widely accepted that lipids, one of the main organic molecules in cells, can cause a number of disorders, including obesity, if they are consumed in excess or are dysregulated.

Because lipids are insoluble, the body needs specialized carriers called lipoproteins to move them throughout [29]. Following digestion, lipids are absorbed by enterocytes and packed in a lipoprotein known as a chylomicron [30]. Lipoprotein Lipase (LPL) interacts with chylomicrons that have been absorbed and hydrolyzes triglyceride (TG) to release glycerol and free fatty acids (FFAs) [31]. The FFAs are absorbed by liver and muscle for either esterification or oxidation after the chylomicron remains are eliminated hepatically [32].

Adipose tissue is affected by hormone sensitive lipase (HSL), which releases FFAs during lipolysis [33], a mechanism that insulin suppresses in fat cells during the fed state [34]. Cholesterol and hepatic TGs may be secreted as a component of extremely low-density lipoproteins (VLDLs). LPL hydrolyzes VLDLs to produce intermediate-density lipoproteins and VLDL

remains (IDLs). IDLs are either absorbed by the liver or converted to LDLs, which are the primary carriers of cholesterol [35]. The liver or peripheral cells absorb LDL [36]. The only method for removing too much cholesterol from peripheral tissue is reverse cholesterol transport (RCT) [37]. RCT depends on high-density lipoproteins (HDLs), which turn peripheral tissue's cholesterol into HDL-C, also known as the "good cholesterol." Hepatocyte cells in the liver absorb the extra cholesterol and expel it into the bile either as bile salts or as free cholesterol following conversion, depending on the peripheral tissue from which it was transferred [38].

No longer are all lipids seen as being the same. It is commonly known that consuming too many saturated fats causes obesity and other disorders to develop. It has already been demonstrated that people with type 2 diabetes who are overweight and have high levels of FFAs, especially saturated fatty acids, in their blood may also have insulin resistance [39]. Insulin resistance develops in obese patients as a result of free fatty acid accumulation in the blood. The pancreas secretes a lot of insulin in order to overcome this resistance, which causes hyperinsulinemia [40]. Increased free fatty acids make it harder for muscles to absorb glucose. Additionally, they activate and deactivate protein kinase which, is found in the liver and muscles, respectively, which increases gluconeogenesis [41].

In addition to its capacity to store lipids, adipose tissue is now understood to be a true organ with both metabolic and endocrine activities. In human research, diet-induced obesity frequently results in metabolic inflammation in the liver and adipose tissue, although both adipose tissue and the liver are susceptible to developing chronic inflammation with ongoing obesity [42]. Obesity and increased insulin resistance associated with chronic inflammation result in aberrant production of adipocytokines like tumor necrosis factor alpha, leptin, interleukin-6, and interleukin-1, and the prothrombotic mediator plasminogen activator inhibitor-1 [Pal-1] [43]. Insulin resistance is caused by oxidative stress, which also prevents adipocytes from generating adiponectin [44].

4.The endocrine function of adipose tissue

Adipose tissue's main purposes are to release free fatty acids during fasting and to retain extra nutrients as triacylglycerols. In addition to serving as the body's primary energy storage organ, adipose tissue is now understood to be an essential endocrine organ that maintains homeostasis [45]. Moreover, numerous cell types, primarily adipocytes, preadipocytes, endothelial cells, and immune cells, can be found in adipose tissue, which produces and secretes a variety of substances known as "adipokines," which are notable for their impact on food patterns and energy homeostasis. Adipose tissue in animals exists in two varieties: brown adipose tissue (BAT) and white adipose tissue (WAT). Both of these adipose tissue types have different functions and anatomical locations. [46].

In people, it is more pronounced in newborns and individuals with high metabolic rates and declines with age and weight gain [47], whereas the WAT mostly stores extra energy. The white adipocyte is a type of cell that is specifically designed for energy storage in the form of triacylglycerols and energy mobilization in mammals as fatty acids. Adipose tissue is crucial for maintaining overall body homeostasis due to adipocyte metabolism. since insulin resistance and related illnesses are mostly caused by white adipocyte metabolic dysfunction [48].

4-1. Adipocytes: hypertrophy and hyperplasia

White adipose tissue, where body fat is deposited, is made up of tiny fat cells called adipocytes, which vary widely in size and number from person to person. Adipose tissue contains pre-adipocytes, which, when stimulated and activated, have the ability to divide and produce new adipocytes. The newly generated white adipocytes will stay in the body till the person dies. Then, they can change in volume but not in number [49]. White adipose tissue enlarges as a result of chronically consuming too much energy, increasing the number of pre-adipocytes (hyperplasia) and the size of adipocytes (hypertrophy) [50]. When an obese person loses weight, the volume of their fat cells decreases due to the loss of a specific quantity of fat, but the number of adipocytes remains constant. Because of this, an obese person who had lost a significant amount of body fat after stopping a crash diet quickly gained it back [51]. Therefore, it's critical to prevent an excessive rise in adipose tissue and the number of adipocytes, especially in youngsters, because this is likely to make them obese for the rest of their lives.

4.2. Secretory factors of adipose tissue

There are numerous different types of cells in WATs, which release many chemicals called adipokines and cytokines [52]. Adiponectin, TGF-beta, IL-1 receptor antagonist, IL-4, 10, 13 are among the anti-inflammatory adipokines that are preferentially secreted by adipose tissue from lean individuals.

However, the majority of proinflammatory cytokines produced by obese adipose tissue are resistin, leptin, angiotensin II, TNF-α, IL-6, visfatin, and plasminogen activator inhibitor 1 (PAI-1) [53]. Anti-inflammatory adipokines mediate physiological processes in lean individuals, but pro-inflammatory adipokines modulate insulin resistance in states of metabolic disease either directly by changing the insulin signaling pathway or indirectly by triggering inflammatory pathways [54].

Leptin is regarded as a key modulator of metabolic and energy homeostasis. It is primarily released by adipose tissue and circulates at levels proportional to body fat mass percentage or abrupt changes in caloric intake. It is seen as a possible indicator of obesity-related problems [55]. It is important to let the central nervous system [CNS] know that the body has too much energy in order to stop eating and start burning energy, Leptin controls the homeostasis of energy. It suppresses hunger and food intake while promoting energy use. Leptin levels are secondary regulated by a number of other factors and are especially sensitive to abrupt changes in caloric intake, declining to 10% to 20% after only 3 days of fasting, far earlier than levels of adipose tissue have been substantially lowered. Only indirectly does leptin function in the peripheral, with its primary action occurring in the brain [56].

Low quantities of leptin are produced in the blood when the lep gene is genetically inactivated in adipose tissue [57]. The main factors affecting blood levels of leptin are fat tissue mass and adipocyte size. These measurements exhibit a strong correlation with leptin production in adipose tissue and its amount in blood circulation. Currently, leptin is thought to be a satiety hormone. When leptin is released into the bloodstream, it travels to the brain and binds to its receptors in the hypothalamus. There, it promotes the inhibition of genes encoding neuropeptide Y (NPY) and the stimulation of genes encoding proomiomelanocortin (POMC) and corticoliberin (CRH). It makes you lose your appetite and eat less, which in turn causes your body fat to go down and your energy use to go up, leading to a loss of body mass [58].

Additionally, leptin may have pro-inflammatory effects because its receptor belongs to the class I cytokine receptor (gp130) superfamily. Pro-inflammatory cytokines increase the production and release of leptin, which in turn helps keep obesity in a state of chronic inflammation [59].

Adiponectin is an essential adipokine that has anti-inflammatory properties. It is the main peptide produced by adipocytes, which are crucial in the development of obesity [60]. Additionally, it serves as a barrier against the progression of serious diseases linked to metabolic disorders and oxidative stress [61]. Adiponectin receptors act as a conduit for the effects of adiponectin [62]. It is generally known that adiponectin increases the liver's and muscles' sensitivity to insulin. It controls the metabolism of fatty acids [63] and peripheral blood glucose [64]. Animal studies have demonstrated that adiponectin increases fat oxidation in muscle and has insulin-sensitizing effects in the liver [65]. In obese people, adiponectin levels are lower [66]. Also, people with lower levels of adiponectin are more resistant to insulin [67]. In mice, adiponectin deficiency causes insulin resistance, whereas adiponectin overexpression enhances insulin sensitivity and glucose tolerance [68].

It is thought that the adiponectin receptors (AdipoR) 1 and 2 have a role in mediating adiponectin's anti-metabolic actions and are reduced in obesity-related insulin resistance [69]. Adiponectin interactions with adiponectin receptors 1 and 2 mediate their effects. AdipoR1 is strongly tied to the activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway, whereas AdipoR2 appears to be connected to the activation of the peroxisome proliferator-activated receptor alpha (PPAR) pathway. Adi-poR1 and Adi-poR2 are mostly expressed in the skeletal muscle and liver, respectively. The primary mechanism by which adiponectin affects the metabolism of skeletal muscle is through activating the AdipoR1-AMPK signaling pathway. It increases insulin sensitivity by promoting glucose absorption and fatty acid oxidation, as well as by promoting the expression of target genes, which increases mitochondrial biogenesis and significantly lowers oxidative stress.

In the pancreas, it makes glucose cause insulin to be released by turning on fatty acid oxidation and stopping beta cells from dying off. In the case of the liver, adiponectin increases fatty acid oxidation while decreasing glucose synthesis, fat accumulation, and fatty acid uptake through activation of the AdipoR2-PPAR signaling pathway; this has the consequence of making the liver more sensitive to insulin. It has the ability to increase glucose absorption and insulin

sensitivity in adipose tissue, and it also has the ability to accelerate the adipogenesis process [70].

Obesity is caused by proinflammatory cytokines that are created during metabolic inflammation; however, these cytokines are also produced during other types of inflammation, such as infection, injury, and autoimmunity. The level of cytokines slightly increases during metabolic inflammation. According to reports, HFD feeding raises IL-6 levels [71]. It means that HFD eating results in low-grade inflammation, which leads to obesity. The cytokines associated with metabolic inflammation are listed in Table 2.

Table 2: The cytokines implicated in metabolic inflammation.

Cytokines promoting obesity		Ref.
TNF-α	TNF- α, lowers energy expenditure while promoting hyperphagia. TNF- α in the hypothalamus rise after consuming a high-fat diet.	[71,72]
IL-4	IL-4 causes inflammation in the hypothalamus and exacerbates the poor metabolism brought on by HFD in rats.	[73]
IL-1β	HFD feeding enhances the production of IL-1 β in the hypothalamus.	[74]
TGFβ	Eating a high-fat diet causes the hypothalamus to produce more TGFβ, which is a mediator of inflammation. Obesity caused by the HFD is prevented by blocking TGFβ signaling.	[75,76]
Resistin	High fat diet feeding causes resistin levels to increase, which mediates inflammation. When resistin signaling is blocked, rats' metabolisms are not affected by high-fat diets.	[77,78]
Cytokines prevent obesity		Ref.
IL-6	IL-6 has pro- and anti-inflammatory effects, although IL-6's role in the hypothalamus is anti-inflammatory.	[79]
IL-18	Mice lacking in IL-18 consumed more food, gained more body fat, and showed insulin resistance.	[80]

5- Obesity-related complications:

Adipose tissue's hemostatic functions are disrupted in abnormal conditions, such as obesity, which leads to dysregulation of the systems required to maintain the stability of the internal environment and the activation of processes that underlie the onset of many metabolic disorders [81]. The metabolic syndrome dramatically raises the risk of insulin resistance, diabetes mellitus, and atherosclerotic cardiovascular disease, which is a composite of multiple disorders (abdominal obesity, hyperglycemia, hypertriglyceridemia, and hypertension) [82].

The basic pathophysiology of obesity mainly comprises an increase in hunger and a decrease in calorie expenditure that can be modified by modifying physical activity and cellular function. These anomalies accelerate the adipogenic process, which accelerates the release of cytokines and vascular problems that cause heart problems like atherosclerosis and hyperlipidemia. The occurrence of secondary illnesses is accompanied by changes in these organs' physiological functions [21].

For example, hepatic steatosis may develop as a result of continuous ectopic fat in the liver [83]. These adipokines are employed in clinical settings to determine if obesity-related disorders exist or not as well as to determine potential therapeutic intervention targets [84]. Some of them have been researched in preclinical studies as pharmacological therapeutic targets and as markers of sickness progression [85]. So, methods that try to shrink the WAT, get rid of hypertrophic adipocytes, turn WAT into BAT, or stop adipogenesis may be the best for treating both obesity and the comorbidities that come with it. Since WAT dysfunction is the main cause of obesity and diseases related to obesity, this tissue makes a lot of adipokines, some of which are linked to obesity [86].

6.Obesity management:

Worldwide, obesity continues to be a serious health issue. Dietary changes and increased activity are effective methods for preventing obesity and excessive weight gain, but because these methods take longer to work, many patients prefer anti-obesity drugs [87]. Anti-obesity medications are used in conjunction with lifestyle changes, surgery, and other methods to maintain a healthy body weight [21]. However, the effectiveness of anti-obesity medications in decreasing body weight is frequently countered by side effects because of their unintended consequences and lack of specificity, which lowers their sensitivity and effectiveness [88].

Therefore, additional efforts should be made to find and create new and improved anti-obesity therapies with long-term efficacy and less adverse effects on healthy tissues.

Plant extracts, in particular, contain antioxidant, anti-inflammatory, and insulin-sensitizing characteristics. Accordingly, several naturally occurring secondary metabolites, including polyphenols, saponins, terpenoids, flavonoids, glycosides, alkaloids, and tannins, are found in various plants and are believed to have anti-obesity activity through a variety of action methods. Numerous bioactive substances found in plants, including green tea containing epigallocatechins, resveratrol, pterostilbene in berries, nobiletin in citrus peel, and curcumin in turmeric, have been documented to inhibit the variables that lead to obesity [89].

6.1. Role of natural products in obesity treatment:

According to various studies, a variety of plant-based extracts with anti-inflammatory, antioxidant, and insulin-sensitizing characteristics have been identified [90]. In the digestive system, enzymes including-amylase, glucosidases, and various lipases that break down carbohydrates and lipids are inhibited by these secondary metabolites. The primary enzymes involved in breaking down carbs into glucose are amylases and glucosidases, which release glucose through glucose transporters [91]. When the amount of sugar in the blood goes above what is considered normal, pancreatic cells eventually release insulin to lower the amount of sugar in the blood [92].

Obesity is caused by the conversion of glucose into lipids and fatty acids, which are then converted into triglycerides and stored in adipose tissue [93]. The digestive process of fatty acids, phospholipids, and triglycerides is carried out mostly by lipases, which are predominantly secreted from various parts of the gastrointestinal system. These enzymes hydrolyze fatty acids, phospholipids, and triglycerides into monoglycerides. These monoglycerides combine with sugars, lysophosphatidic acid, and bile salts to create chylomicrons and the micellar structure. Triglycerides are then produced and stored in adipose tissue as a result of this structure entering enterocytes [94].

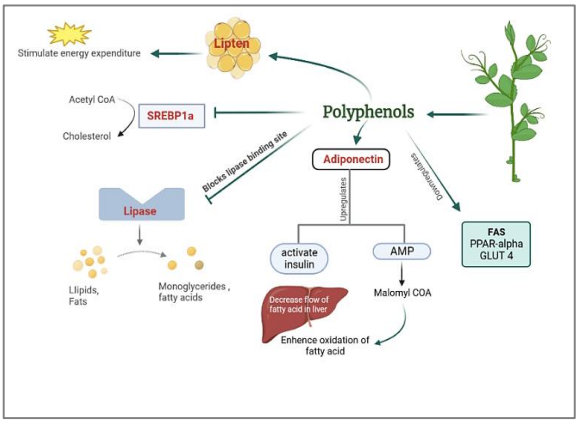

Fig. 1. Diagram displaying the several processes in the treatment of obesity that are mostly controlled by polyphenols.

Obesity is finally decreased as a result of the inhibition of these enzymes following administration of plant-based products. By changing the levels of hormones like leptin, ghrelin, and insulin, these secondary metabolites also help people who are overweight lose weight. Leptin is mostly made by the WAT. When its receptors in the CNS are activated, leptin controls the "brain-gut axis" by reducing food intake and making it easier to burn calories [95]. Insulin is released by the pancreatic beta cells, and it changes brain signals to cause a long-term reduction in food consumption and an increase in energy expenditure. Leptin and insulin both provide signals that cooperate to lower food [96]. Both hormone levels are elevated by anti-obesity plants.

Adipokine, which is also released from adipose tissue, stimulates hepatic insulin activity, promotes fatty acid oxidation, and improves skeletal muscle and liver glucose uptake [95]. It is primarily activated by AMPK, which blocks acetyl-CoA carboxylase activity and lowers the amount of malonyl-CoA in the body [97]. Also, stopping the release of ghrelin, which is often called the "hunger hormone," can help fight obesity [98].

Numerous transcriptional variables involved in different stages of adipogenesis and adipocyte differentiation can be managed to reduce obesity [99]. These transcriptional regulators include proliferator-activated receptors (PPAR), sterol regulatory elementary binding proteins (SREBP), and CCAAT/enhancer binding proteins (C/EBP) [100].

The management of obesity by various plant metabolites also includes repression at the levels of SREBP [101] and C/EBP [102] and augmentation of the PPAR level [103]. By controlling how lipids are made and broken down, the negative effects of being overweight can be mitigated by several enzymes and hormones [104]. The major regulators of the process of cholesterol production from acetyl CoA are LDL, SREBP1a, SREBP2, and receptor 3-hydroxy-3-methylglutaryl CoA reductase [105]. Stearoyl CoA desaturase and fatty acid synthase (FAS) are lipogenic enzymes whose transcription is turned up by SREBP-1c [106].

Amplification of AMPK inhibits the synthesis of fatty acids and cholesterol via interfering with SREBP-1c and FAS [107]. Similar to this, fatty acid oxidation is accelerated and hepatic triglyceride levels are reduced by carnitine palmitoyl transferase 1A (CPT1A) [108]. Therefore, controlling all of these factors has a positive impact on avoiding obesity by using natural products, which are secondary metabolites derived from plants. the main methods through which polyphenols exert anti-obesity actions are depicted in Figs. 1, (109). Additionally, Table 3 details the role of several plants in the treatment of obesity.

6.2. Role of nanotechnology in obesity treatment*:*

The transport and bioavailability of plant-derived bioactive chemicals are always problematic, despite substantial research on their medicinal effects. Nanotechnology is one of the promising methods for increasing therapeutic efficacy while decreasing side effects. The bioavailability, biodistribution, stability, and solubility of natural chemicals are improved by nanotechnology, making it a promising phenomenon for the treatment of specific disorders. The pharmaceutical and medical industries have seen a transformation in recent years as a result of the

nanoencapsulation of bioactive substances. These nanosystems have enhanced the bioavailability of plant extracts. It is anticipated that these plant extract-encapsulated nano-formulations may cause some metabolic alterations [17].

Table 3: A variety of plants having anti-obesity properties.

Plant or [Secondary Metabolite]	Experimental Model	Important Findings		Ref.
		Decreased level	Increased level	
Rhizome of Curcuma longa [Curcumin]	Sprague-Dawley rats	PPAR-γ, C/EBPα, FAS, ACC TG, LDL Body weight	AMPK Adiponectin CPT1	[110]
Leaves of Gymenma sylvestra [Deacyl gymnemic acid]	C57BL/6J mice	Body weight TC, TG, LDL Leptin	HDL	[111]
Seeds of Capsicum annuum [Capsicoside G-rich protein]	C57BL/6J mice	Body weight, TG, TC, AST, ALT C/EBPα,, PPARγSREBP1c, FAS		[112]
Fruit of Diospyros kaki and peel of Citrus unshui [Flavonoids and phenolic compounds]	Mice	Body weight TC, TG, LDL	HDL	[113]
Leaves of Cirsium setidens [Pectolinarin]	C57BL/6J mice	Expression of PPARα, C/EBPα, C/EBP-δ, body weight, AST, ALT, TC, TG	-	[114]
Leaves of Cosmos cadatus Kunth [Catechins, quercetin]	Sprague-Dawley rats	Body weight Ghrelin leptin AST, ALT, ALP	-	[115]
Seeds oil of Moringa olifera [Tannins, flavonoids, terpenoids, and saponins]	Sprague-Dawley rats	Body weight, Kidney weight Creatinine, uric acid TC, ALT, AST,	-	[116]
Seeds of Theobroma cocao [Proteins isolated; Vicillin and albumin]	Male wistar rats	Body weight Total lipids, TG, TC	-	[117]
Soybean embryo [Isoflavones]	Mice	Body weight lipids contents	Expression of HSL, UCP1, CREB, SIRT1	[118]
Diosgenin	adult male C57BL/6J mice	Body weight, ALT; AST, TG, TC expression of SREBP-1C, FASN gene	HDL TAC	[119]

Nanoparticles (ANPs) might provide us a brand-new, helpful mediator in the prevention and treatment of obesity. Plant extracts have been utilized to create a wide range of nano-drug delivery systems, including liposomes, solid lipids, hydrogel nanocomposites, nano-emulsions, micelles, and core-shell nanoparticles. Nanotechnology refers to the chemical and physical synthesis of materials with nano-sizes between 1 and 100 nm [120]. Several previous studies on animal models have revealed that biogenic ANPs have anti-obesity and antioxidant properties [121]. The majority of nano-formulations successfully decreased oxidative stress, insulin resistance, lipid profiles, and chronic inflammation in vivo and in vitro investigations as a result of the fact that plant extracts interfere with metabolic syndrome pathways. Therefore, these innovative plant-based nano-systems could be a good candidate for medical applications [17]. Table 4 outlines the function of plant-derived nanosystems for lowering obesity.

Table 4: Nanosystems for obesity derived from plant extracts.

Medicinal plants	Nano-systems	Experimental models	Important Findings	Ref.
Oleoresin capsicum	Alginate double-layer nanoemulsion & single-layer nanoemulsion	HFD-induced obesity in rat, 3T3- L1 cell lines	Decrease in level of Lipid,TGs, fatty Acid-binding protein, PPAR- γ	[122]
Citrus sinensis	Nano-vesicles	HFHSD mice	Decrease in level of plasma lipids, Chylomicron synthesis, TGs	[123]
Dendropanax morbifera	Gold nanoparticles	HepG2 &3T3-L1 cell lines	Decrease in level of TGs, PPAR- γ	[121]
Saponins, flavonoids and proanthocya-nidins	Gold nanoparticles of Salacia chinensis	Rat	Decrease in level of BMI, AMPKα1, pAMPKα1 Adipose index, resistin, leptin Increase in level of Adiponectin	[19]
Succinyl chitosanalgina te- core shell NPs	Nano-encapsulated Quercetin	Male wistar rat	Decrease in level of, TG, TC, AST, ALT. ALP	[124]
Turmeric loaded nanoemulsion	Nano-encapsulated curcumin	HepG2 cells & Balb/c mice	Decrease in level of, PPARγ, TC, TG, SREBP-1	[125]

7- Conclusions

Obesity is a serious, common illness linked to higher rates of morbidity and mortality. It increases a person's risk of developing a wide range of pathological consequences, including coronary heart disease, stroke, liver cirrhosis, type 2 diabetes, several different cancer types, and hypertension. In addition, it is defined as "chronic low-grade inflammation and oxidative stress" and linked to numerous metabolic dysfunctions. A successful treatment strategy is necessary to address the issues with obesity's pathogenesis. Anti-obesity medications are used in conjunction with lifestyle changes, surgery, and other methods to retain a healthy weight. However, the effectiveness of anti-obesity medications in decreasing body weight is frequently countered by side effects because of their unintended consequences and lack of specificity, which lowers their sensitivity and effectiveness. Therefore, bioactive substances from plants exhibit anti-obesity activities primarily by impeding the enzymes that break down lipids and carbohydrates, suppressing adipogenesis and adiponectin, and enhancing energy metabolism. These natural chemicals' ability to alleviate obesity-related comorbidities is improved by nanotechnology.

8- References:

[1] Leal-Ugarte, E., Peralta-Leal, V., Meza-Espinoza, J. P., Durán-González, J., Macias-Gomez, N., Bocanegra-Alonso, A., & Lara-Ramos, J. R. [2019]. Association of the MTHFR 677C> T polymorphism with obesity and biochemical

variables in a young population of Mexico. Journal of Medical Biochemistry, 38[4], 461.
[2] Medina, D. A., Li, T., Thomson, P., Artacho, A., Perez-Brocal, V., & Moya, A. [2019]. Cross-regional view of functional and taxonomic microbiota composition in obesity and post-obesity treatment shows country specific microbial contribution. Frontiers in microbiology, 10, 2346.
[3] Jéquier, E. [2002]. Pathways to obesity. International Journal of Obesity, 26[2], S12-S17.
[4] Al-Nbaheen, M. S. [2020]. Impact of weight loss predictors in severe-morbid obesity patients in the Saudi population. Saudi Journal of Biological Sciences, 27[10], 2509-2513.
[5] Rychter, A. M., Zawada, A., Ratajczak, A. E., Dobrowolska, A., & Krela-Kaźmierczak, I. [2020]. Should patients with obesity be more afraid of COVID-19?. Obesity reviews, 21[9], e13083.
[6] Goodarzi, M. O. [2018]. Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications. The lancet Diabetes & endocrinology, 6[3], 223-236.
[7] Zhang, X., Zhang, G., Zhang, H., Karin, M., Bai, H., & Cai, D. [2008]. Hypothalamic IKKβ/NF-κB and ER stress link overnutrition to energy imbalance and obesity. Cell, 135[1], 61-73.
[8] Rodrigues, A. L., de Moura, E. G., Passos, M. C. F., Trevenzoli, I. H., da Conceição, E. P. S., Bonono, I. T., ... & Lisboa, P. C. [2011]. Postnatal early overfeeding induces hypothalamic higher SOCS3 expression and lower STAT3 activity in adult rats. The Journal of nutritional biochemistry, 22[2], 109-117.
[9] Blackwell, D. L., Lucas, J. W., & Clarke, T. C. [2014]. Summary health statistics for US adults: national health interview survey, 2012. Vital and health statistics. Series 10, Data from the National Health Survey, [260], 1-161.
[10] Park, S., Jang, A., & Bouret, S. G. [2020]. Maternal obesity-induced endoplasmic reticulum stress causes metabolic alterations and abnormal hypothalamic development in the offspring. PLoS biology, 18[3], e3000296.
[11] Fatima, Y., Doi, S. A., & Mamun, A. A. [2016]. Sleep quality and obesity in young subjects: a meta-analysis. Obesity reviews, 17[11], 1154-1166.
[12] Darbre, P. D. [2017]. Endocrine Disruptors and Obesity. Curr. Obes. Rep. 6, 18–27.
[13] Riveros-McKay, F., Mistry, V., Bounds, R., Hendricks, A., Keogh, J. M., Thomas, H., & Farooqi, I. S. [2019]. Genetic architecture of human thinness compared to severe obesity. PLoS genetics, 15[1], e1007603.
[14] Wang, S. B., & Cho, Y. C. [2011]. Body mass index and subsequent risk of hypertension, hyperglycemia and hypercholesterolemia in health checkup examinees. Journal of the Korea academia-industrial cooperation society, 12[6], 2677-2684.
[15] Xiao, S., Zhang, Z., Chen, M., Zou, J., Jiang, S., Qian, D., & Duan, J. [2019]. Xiexin Tang ameliorates dyslipidemia in high-fat diet-induced obese rats via elevating gut microbiota-derived short chain fatty acids production and adjusting energy metabolism. Journal of ethnopharmacology, 241, 112032.
[16] Kusminski, C. M., Bickel, P. E., & Scherer, P. E. [2016]. Targeting adipose tissue in the treatment of obesity-associated diabetes. Nature reviews Drug discovery, 15[9], 639-660.
[17] Hu, F., Sun, D. S., Wang, K. L., & Shang, D. Y. [2021]. Nanomedicine of Plant Origin for the Treatment of Metabolic Disorders. Frontiers in Bioengineering and Biotechnology, 9.
[18] Izadi, V., Haghighatdoost, F., Moosavian, P., & Azadbakht, L. [2018]. Effect of low-energy-dense diet rich in multiple functional foods on weight-loss maintenance, inflammation, and cardiovascular risk factors: a randomized controlled trial. Journal of the American College of Nutrition, 37[5], 399-405.
[19] Gao, L., Hu, Y., Hu, D., Li, Y., Yang, S., Dong, X., Alharbi, S. & Liu, H. [2020]. Anti-obesity activity of gold nanoparticles synthesized from Salacia chinensis modulates the biochemical alterations in high-fat diet-induced obese rat model via AMPK signaling pathway. Arabian Journal of Chemistry, 13[8], 6589-6597.
[20] Bray, G. A., Heisel, W. E., Afshin, A., Jensen, M. D., Dietz, W. H., Long, M., ... & Inge, T. H. [2018]. The science of obesity management: an endocrine society scientific statement. Endocrine reviews, 39[2], 79-132.
[21] Leitner, D. R., Frühbeck, G., Yumuk, V., Schindler, K., Micic, D., Woodward, E., & Toplak, H. [2017]. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies-EASO can lead the way. Obesity facts, 10[5], 483-492.
[22] Hoffman, D., Powell, T., Barrett, E. & Hardy, D., [2021]. Developmental origins of metabolic diseases. Physiological Reviews, 101[3], pp.739-795.
[23] Fairbrother, U., Kidd, E., Malagamuwa, T., & Walley, A. [2018]. Genetics of severe obesity. Current diabetes reports, 18[10], 1-9.
[24] Lin, X., & Li, H. [2021]. Obesity: epidemiology, pathophysiology, and therapeutics. Frontiers in endocrinology, 1070.
[25] Rahayu, E. P., Handayani, N., & Rizki, L. K. [2021]. PENGARUH POSITIVE AFFIRMATION TERHADAP MASALAH MAKAN PADA ANAK. Medika Respati: Jurnal Ilmiah Kesehatan, 16[4], 257-262.
[26] Cecchini, M., & Vuik, S. [2019]. The heavy burden of obesity.
[27] Kesh, S. B., Sarkar, D. E. B. A. S. H. R. E. E., & Manna, K. R. I. S. H. N. E. N. D. U. [2016]. High-fat diet-induced oxidative stress and its impact on metabolic syndrome: a review. Asian J Pharm Clin Res, 9[1], 47-52.
[28] Hohos, N. M., & Skaznik-Wikiel, M. E. [2017]. High-fat diet and female fertility. Endocrinology, 158[8], 2407-2419.
[29] Mahley, R. W., Innerarity, T. L., Rall Jr, S. C., & Weisgraber, K. H. [1984]. Plasma lipoproteins: apolipoprotein structure and function. Journal of lipid research, 25[12], 1277-1294.
[30] Hussain, M. M., Kedees, M. H., Singh, K., Athar, H., & Jamali, N. Z. [2001]. Signposts in the

assembly of chylomicrons. Frontiers in Bioscience-Landmark, 6[3], 320-331.
[31] Kersten, S., [2014]. Physiological regulation of lipoprotein lipase. Biochimica et Biophysica Acta [BBA] - Molecular and Cell Biology of Lipids, 1841[7], pp.919-933.
[32] Wagenmakers, A. J., Frayn, K. N., Arner, P., & Yki-Järvinen, H. [2006]. Fatty acid metabolism in adipose tissue, muscle and liver in health and disease. Essays in biochemistry, 42, 89-103.
[33] Lampidonis, A. D., Rogdakis, E., Voutsinas, G. E., & Stravopodis, D. J. [2011]. The resurgence of Hormone-Sensitive Lipase [HSL] in mammalian lipolysis. Gene, 477[1-2], 1-11.
[34] Arner, P., Bernard, S., Salehpour, M., Possnert, G., Liebl, J., Steier, P., ... & Spalding, K. L. [2011]. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature, 478[7367], 110-113.
[35] Shelness, G. S., & Sellers, J. A. [2001]. Very-low-density lipoprotein assembly and secretion. Current opinion in lipidology, 12[2], 151-157.
[36] Spady, D. K., Turley, S. D., & Dietschy, J. M. [1985]. Receptor-independent low density lipoprotein transport in the rat in vivo. Quantitation, characterization, and metabolic consequences. The Journal of clinical investigation, 76[3], 1113-1122.
[37] Groen, A., Oude Elferink, R., Verkade, H., & Kuipers, F. [2004]. The ins and outs of reverse cholesterol transport. Annals of medicine, 36[2], 135-145.
[38] Rader, D. J., Alexander, E. T., Weibel, G. L., Billheimer, J., & Rothblat, G. H. [2009]. The role of reverse cholesterol transport in animals and humans and relationship to atherosclerosis. Journal of lipid research, 50, S189-S194.
[39] Cena, H., & Calder, P. C. [2020]. Defining a healthy diet: evidence for the role of contemporary dietary patterns in health and disease. Nutrients, 12[2], 334.
[40] Oh, Y. S., Bae, G. D., Baek, D. J., Park, E. Y., & Jun, H. S. [2018]. Fatty acid-induced lipotoxicity in pancreatic beta-cells during development of type 2 diabetes. Frontiers in endocrinology, 9, 384.
[41] Rochlani, Y., Pothineni, N. V., Kovelamudi, S., & Mehta, J. L. [2017]. Metabolic syndrome: pathophysiology, management, and modulation by natural compounds. Therapeutic advances in cardiovascular disease, 11[8], 215-225.
[42] van der Heijden, R. A., Sheedfar, F., Morrison, M. C., Hommelberg, P. P., Kor, D., Kloosterhuis, N. J., ... & Heeringa, P. [2015]. High-fat diet induced obesity primes inflammation in adipose tissue prior to liver in C57BL/6j mice. Aging [Albany NY], 7[4], 256.
[43] Di Lorenzo, C., Dell'Agli, M., Colombo, E., Sangiovanni, E., & Restani, P. [2013]. Metabolic syndrome and inflammation: a critical review of in vitro and clinical approaches for benefit assessment of plant food supplements. Evidence-Based Complementary and Alternative Medicine, 1-10.
[44] Furukawa, S., Fujita, T., Shimabukuro, M., Iwaki, M., Yamada, Y., Nakajima, Y., ... & Shimomura, I. [2017]. Increased oxidative stress in obesity and its impact on metabolic syndrome. The Journal of clinical investigation, 114[12], 1752-1761.
[45] Lee, P., Greenfield, J. R., Ho, K. K., & Fulham, M. J. [2010]. A critical appraisal of the prevalence and metabolic significance of brown adipose tissue in adult humans. American Journal of Physiology-Endocrinology and Metabolism, 299[4], E601-E606.
[46] Vargas-Castillo, A., Fuentes-Romero, R., Rodriguez-Lopez, L. A., Torres, N., & Tovar, A. R. [2017]. Understanding the biology of thermogenic fat: is browning a new approach to the treatment of obesity?. Archives of medical research, 48[5], 401-413.
[47] Giordano, A., Frontini, A., & Cinti, S. [2016]. Convertible visceral fat as a therapeutic target to curb obesity. Nature Reviews Drug Discovery, 15[6], 405-424.
[48] Morigny, P., Boucher, J., Arner, P., & Langin, D. [2021]. Lipid and glucose metabolism in white adipocytes: pathways, dysfunction and therapeutics. Nature Reviews Endocrinology, 17[5], 276-295.
[49] Ali, A. T., Hochfeld, W. E., Myburgh, R., & Pepper, M. S. [2013]. Adipocyte and adipogenesis. European journal of cell biology, 92[6-7], 229-236.
[50] Kwok, K. H., Lam, K. S., & Xu, A. [2016]. Heterogeneity of white adipose tissue: molecular basis and clinical implications. Experimental & molecular medicine, 48[3], e215-e215.
[51] Divella, R., De Luca, R., Abbate, I., Naglieri, E., & Daniele, A. [2016]. Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. Journal of Cancer, 7[15], 2346.
[52] Ràfols, M. E. [2014]. Adipose tissue: cell heterogeneity and functional diversity. Endocrinología y Nutrición [English Edition], 61[2], 100-112.
[53] Ouchi, N., Parker, J. L., Lugus, J. J., & Walsh, K. [2011]. Adipokines in inflammation and metabolic disease. Nature reviews immunology, 11[2], 85-97.
[54] Tilg, H., & Moschen, A. [2008]. Inflammatory Mechanisms in the Regulation of Insulin Resistance. Molecular Medicine, 14[3-4], 222-231.
[55] Jin, D., Sun, J., Huang, J., He, Y., Yu, A., Yu, X., & Yang, Z. [2014]. TNF-α reduces g0s2 expression and stimulates lipolysis through PPAR-γ inhibition in 3T3-L1 adipocytes. Cytokine, 69[2], 196-205.
[56] Odle, A. K., Haney, A., Allensworth-James, M., Akhter, N., & Childs, G. V. [2014]. Adipocyte versus pituitary leptin in the regulation of pituitary hormones: somatotropes develop normally in the absence of circulating leptin. Endocrinology, 155[11], 4316-4328.
[57] Al-Shukaili, A., Al-Ghafri, S., Al-Marhoobi, S., Al-Abri, S., Al-Lawati, J., & Al-Maskari, M. [2013]. Analysis of inflammatory mediators in type 2 diabetes patients. International journal of endocrinology, 2013.
[58] Halcox, J. P., Roy, C., Tubach, F., Banegas, J. R., Dallongeville, J., De Backer, G., ... & Borghi, C. [2014]. C-reactive protein levels in patients at cardiovascular risk: EURIKA study. BMC cardiovascular disorders, 14[1], 1-9.

[59] Tumminia, A., Vinciguerra, F., Parisi, M., Graziano, M., Sciacca, L., Baratta, R., & Frittitta, L. [2019]. Adipose tissue, obesity and adiponectin: role in endocrine cancer risk. International journal of molecular sciences, 20[12], 2863.
[60] Becic, T., Studenik, C., & Hoffmann, G. [2018]. Exercise increases adiponectin and reduces leptin levels in prediabetic and diabetic individuals: systematic review and meta-analysis of randomized controlled trials. Medical sciences, 6[4], 97.
[61] Wang, Y., Meng, R. W., Kunutsor, S. K., Chowdhury, R., Yuan, J. M., Koh, W. P., & Pan, A. [2018]. Plasma adiponectin levels and type 2 diabetes risk: a nested case-control study in a Chinese population and an updated meta-analysis. Scientific reports, 8[1], 1-13.
[62] Ruan, H., & Dong, L. Q. [2016]. Adiponectin signaling and function in insulin target tissues. Journal of molecular cell biology, 8[2], 101-109.
[63] Yanai, H., & Yoshida, H. [2019]. Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. International journal of molecular sciences, 20[5], 1190.
[64] Stern, J. H., Rutkowski, J. M., & Scherer, P. E. [2016]. Adiponectin, leptin, and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell metabolism, 23[5], 770-784.
[65] Dıez, J. J., & Iglesias, P. [2003]. The role of the novel adipocyte-derived hormone adiponectin in human disease. Eur J Endocrinol, 148[3], 293-300.
[66] Arita, Y., Kihara, S., Ouchi, N., Takahashi, M., Maeda, K., Miyagawa, J. I., ... & Matsuzawa, Y. [1999]. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochemical and biophysical research communications, 257[1], 79-83.
[67] Kern, P. A., Di Gregorio, G. B., Lu, T., Rassouli, N., & Ranganathan, G. [2003]. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-α expression. Diabetes, 52[7], 1779-1785.
[68] Maeda, N., Shimomura, I., Kishida, K., Nishizawa, H., Matsuda, M., Nagaretani, H., . & Matsuzawa, Y. [2002]. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nature medicine, 8[7], 731-737.
[69] Kadowaki, T., Yamauchi, T., Kubota, N., Hara, K., Ueki, K., & Tobe, K. [2006]. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. The Journal of clinical investigation, 116[7], 1784-1792.
[70] Howlader, M., Sultana, M. I., Akter, F., & Hossain, M. M. [2021]. Adiponectin gene polymorphisms associated with diabetes mellitus: A descriptive review. Heliyon, 7[8], e07851.
[71] Valdearcos, M., Robblee, M. M., Benjamin, D. I., Nomura, D. K., Xu, A. W., & Koliwad, S. K. [2014]. Microglia dictate the impact of saturated fat consumption on hypothalamic inflammation and neuronal function. Cell reports, 9[6], 2124-2138.
[72] Arruda, A. P., Milanski, M., Coope, A., Torsoni, A. S., Ropelle, E., Carvalho, D. P., ... & Velloso, L. A. [2011]. Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. Endocrinology, 152[4], 1314-1326.
[73] Oh-I, S., Thaler, J. P., Ogimoto, K., Wisse, B. E., Morton, G. J., & Schwartz, M. W. (2010). Central administration of interleukin-4 exacerbates hypothalamic inflammation and weight gain during high-fat feeding. American Journal of Physiology-Endocrinology and Metabolism, 299(1), E47-E53.
[74] Osborn, O., Brownell, S. E., Sanchez-Alavez, M., Salomon, D., Gram, H., & Bartfai, T. (2008). Treatment with an Interleukin 1 beta antibody improves glycemic control in diet-induced obesity. Cytokine, 44(1), 141-148.
[75] Yan, J., Zhang, H., Yin, Y., Li, J., Tang, Y., Purkayastha, S., ... & Cai, D. (2014). Obesity-and aging-induced excess of central transforming growth factor-β potentiates diabetic development via an RNA stress response. Nature medicine, 20(9), 1001-1008.
[76] Mendes, N. F., Gaspar, J. M., Lima-Júnior, J. C., Donato Jr, J., Velloso, L. A., & Araújo, E. P. (2018). TGF-β1 down-regulation in the mediobasal hypothalamus attenuates hypothalamic inflammation and protects against diet-induced obesity. Metabolism, 85, 171-182.
[77] Muse, E. D., Obici, S., Bhanot, S., Monia, B. P., McKay, R. A., Rajala, M. W., ... & Rossetti, L. (2004). Role of resistin in diet-induced hepatic insulin resistance. The Journal of clinical investigation, 114(2), 232-239.
[78] Singhal, N. S., Lazar, M. A., & Ahima, R. S. (2007). Central resistin induces hepatic insulin resistance via neuropeptide Y. Journal of Neuroscience, 27(47), 12924-12932.
[79] Timper, K., Denson, J. L., Steculorum, S. M., Heilinger, C., Engström-Ruud, L., Wunderlich, C. M., ... & Brüning, J. C. (2017). IL-6 improves energy and glucose homeostasis in obesity via enhanced central IL-6 trans-signaling. Cell reports, 19(2), 267-280.
[80] Zorrilla, E. P., Sanchez-Alavez, M., Sugama, S., Brennan, M., Fernandez, R., Bartfai, T., & Conti, B. (2007). Interleukin-18 controls energy homeostasis by suppressing appetite and feed efficiency. Proceedings of the National Academy of Sciences, 104(26), 11097-11102.
[81] Zorena, K., Jachimowicz-Duda, O., & Wąż, P. (2016). The cut-off value for interleukin 34 as an additional potential inflammatory biomarker for the prediction of the risk of diabetic complications. Biomarkers, 21(3), 276-282.
[82] Wang, H. H., Lee, D. K., Liu, M., Portincasa, P., & Wang, D. Q. (2020). Novel insights into the pathogenesis and management of the metabolic syndrome. Pediatric Gastroenterology, Hepatology & Nutrition. 23(3),189–230.
[83] Nassir, F., Rector, R. S., Hammoud, G. M., & Ibdah, J. A. (2015). Pathogenesis and prevention of hepatic steatosis. Gastroenterology & hepatology, 11(3), 167.
[84] Miyamoto, S., & Sharma, K. (2013). Adipokines protecting CKD. Nephrology dialysis transplantation, 28(suppl_4), iv15-iv22.
[85] Zhang, Y., Liu, Q., Yu, J., Yu, S., Wang, J., Qiang, L., & Gu, Z. (2017). Locally induced

adipose tissue browning by microneedle patch for obesity treatment. ACS nano, 11(9), 9223-9230.
[86] Lee, J. J., Britton, K. A., Pedley, A., Massaro, J. M., Speliotes, E. K., Murabito, J. M., ... & Fox, C. S. (2016). Adipose tissue depots and their cross-sectional associations with circulating biomarkers of metabolic regulation. Journal of the American Heart Association, 5(5), e002936.
[87] Urbatzka, R., Freitas, S., Palmeira, A., Almeida, T., Moreira, J., Azevedo, C., ... & Vasconcelos, V. (2018). Lipid reducing activity and toxicity profiles of a library of polyphenol derivatives. European journal of medicinal chemistry, 151, 272-284.
[88] Sellayah, D., Cagampang, F. R., & Cox, R. D. (2014). On the evolutionary origins of obesity: a new hypothesis. Endocrinology, 155(5), 1573-1588.
[89] Huang, L., Chen, J., Cao, P., Pan, H., Ding, C., Xiao, T., ... & Su, Z. (2015). Anti-obese effect of glucosamine and chitosan oligosaccharide in high-fat diet-induced obese rats. Marine Drugs, 13(5), 2732-2756.
[90] Naseri, R., Farzaei, F., Haratipour, P., Nabavi, S. F., Habtemariam, S., Farzaei, M. H., ... & Momtaz, S. (2018). Anthocyanins in the management of metabolic syndrome: A pharmacological and biopharmaceutical review. Frontiers in Pharmacology, 9, 1310.
[91] Nyambe-Silavwe, H., Villa-Rodriguez, J. A., Ifie, I., Holmes, M., Aydin, E., Jensen, J. M., & Williamson, G. (2015). Inhibition of human α-amylase by dietary polyphenols. Journal of Functional Foods, 19, 723-732.
[92] Wong, S. K., Chin, K. Y., Suhaimi, F. H., Fairus, A., & Ima-Nirwana, S. (2016). Animal models of metabolic syndrome: a review. Nutrition & metabolism, 13(1), 1-12.
[93] Duwaerts, C. C., & Maher, J. J. (2019). Macronutrients and the adipose-liver axis in obesity and fatty liver. Cellular and molecular gastroenterology and hepatology, 7(4), 749-761.
[94] Birari, R. B., & Bhutani, K. K. (2007). Pancreatic lipase inhibitors from natural sources: unexplored potential. Drug discovery today, 12(19-20), 879-889.
[95] Singla, P., Bardoloi, A., & Parkash, A. A. (2010). Metabolic effects of obesity: a review. World journal of diabetes, 1(3), 76.
[96] Ashrafi, K. (2007). Obesity and the regulation of fat metabolism. WormBook: The Online Review of C. elegans Biology [Internet].
[97] Yamauchi, T., Kamon, J., Minokoshi, Y. A., Ito, Y., Waki, H., Uchida, S., ... & Kadowaki, T. (2002). Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nature medicine, 8(11), 1288-1295.
[98] Santiago-García, P. A., & López, M. G. (2014). Agavins from Agave angustifolia and Agave potatorum affect food intake, body weight gain and satiety-related hormones (GLP-1 and ghrelin) in mice. Food & Function, 5(12), 3311-3319.
[99] Lefterova, M. I., & Lazar, M. A. (2009). New developments in adipogenesis. Trends in Endocrinology & Metabolism, 20(3), 107-114.
[100] Brey, C. W., Nelder, M. P., Hailemariam, T., Gaugler, R., & Hashmi, S. (2009). Krüppel-like family of transcription factors: an emerging new frontier in fat biology. International journal of biological sciences, 5(6), 622.
[101] Choi, R. Y., Nam, S. J., Ham, J. R., Lee, H. I., Yee, S. T., Kang, K. Y., ... & Lee, M. K. (2016). Anti-adipogenic and anti-diabetic effects of cis-3′, 4′-diisovalerylkhellactone isolated from Peucedanum japonicum Thunb leaves in vitro. Bioorganic & Medicinal Chemistry Letters, 26(19), 4655-4660.
[102] Imran, A., Butt, M. S., Arshad, M. S., Arshad, M. U., Saeed, F., Sohaib, M., & Munir, R. (2018). Exploring the potential of black tea based flavonoids against hyperlipidemia related disorders. Lipids in health and disease, 17(1), 1-16.
[103] Tan, S., Gao, B., Tao, Y., Guo, J., & Su, Z. Q. (2014). Antiobese effects of capsaicin–chitosan microsphere (CCMS) in obese rats induced by high fat diet. Journal of agricultural and food chemistry, 62(8), 1866-1874.
[104] Wang, L., Zeng, B., Liu, Z., Liao, Z., Zhong, Q., Gu, L., ... & Fang, X. (2018). Green tea polyphenols modulate colonic microbiota diversity and lipid metabolism in high-fat diet treated HFA mice. Journal of food science, 83(3), 864-873.
[105] Karagianni, P., & Talianidis, I. (2015). Transcription factor networks regulating hepatic fatty acid metabolism. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids, 1851(1), 2-8.
[106] Salvado, L., Palomer, X., Barroso, E., & Vázquez-Carrera, M. (2015). Targeting endoplasmic reticulum stress in insulin resistance. Trends in Endocrinology & Metabolism, 26(8), 438-448.
[107] Srivastava, R. A. K., Pinkosky, S. L., Filippov, S., Hanselman, J. C., Cramer, C. T., & Newton, R. S. (2012). AMP-activated protein kinase: an emerging drug target to regulate imbalances in lipid and carbohydrate metabolism to treat cardio-metabolic diseases: thematic review series: new lipid and lipoprotein targets for the treatment of cardiometabolic diseases. Journal of lipid research, 53(12), 2490-2514.
[108] Takei, K., Nakagawa, Y., Wang, Y., Han, S. I., Satoh, A., Sekiya, M., ... & Shimano, H. (2017). Effects of K-877, a novel selective PPARα modulator, on small intestine contribute to the amelioration of hyperlipidemia in low-density lipoprotein receptor knockout mice. Journal of pharmacological sciences, 133(4), 214-222.
[109] Bhardwaj M, Yadav P, Vashishth D, Sharma K, Kumar A, Chahal J, ... & Kataria SK. 2021. A review on obesity management through natural compounds and a green nanomedicine-based approach. Molecules, 26(11), 3278.
[110] Kim, J. H., Kim, O. K., Yoon, H. G., Park, J., You, Y., Kim, K., ... & Jun, W. (2016). Anti-obesity effect of extract from fermented Curcuma longa L. through regulation of adipogenesis and lipolysis pathway in high-fat diet-induced obese rats. Food & nutrition research, 60(1), 30428.
[111] Kim, H. J., Hong, S. H., Chang, S. H., Kim, S., Lee, A. Y., Jang, Y., ... & Cho, M. H. (2016). Effects of feeding a diet containing Gymnema sylvestre extract: Attenuating progression of

obesity in C57BL/6J mice. Asian Pacific Journal of Tropical Medicine, 9(5), 437-444.
[112] Sung, J., Jeong, H. S., & Lee, J. (2016). Effect of the capsicoside G-rich fraction from pepper (capsicum annuum L.) seeds on high-fat diet-induced obesity in mice. Phytotherapy Research, 30(11), 1848-1855.
[113] Kim, G. N., Shin, M. R., Shin, S. H., Lee, A. R., Lee, J. Y., Seo, B. I., ... & Roh, S. S. (2016). Study of antiobesity effect through inhibition of pancreatic lipase activity of Diospyros kaki fruit and Citrus unshiu peel. BioMed research international.
[114] Cho, B. Y., Park, M. R., Lee, J. H., Ra, M. J., Han, K. C., Kang, I. J., & Lee, O. H. (2017). Standardized Cirsium setidens Nakai ethanolic extract suppresses adipogenesis and regulates lipid metabolisms in 3T3-L1 adipocytes and C57BL/6J mice fed high-fat diets. Journal of medicinal food, 20(8), 763-776.
[115] Rahman, H. A., Sahib, N. G., Saari, N., Abas, F., Ismail, A., Mumtaz, M. W., & Hamid, A. A. (2017). Anti-obesity effect of ethanolic extract from Cosmos caudatus Kunth leaf in lean rats fed a high fat diet. BMC complementary and alternative medicine, 17(1), 1-17.
[116] Kilany, O. E., Abdelrazek, H. M., Aldayel, T. S., Abdo, S., & Mahmoud, M. M. (2020). Anti-obesity potential of Moringa olifera seed extract and lycopene on high fat diet induced obesity in male Sprauge Dawely rats. Saudi Journal of Biological Sciences, 27(10), 2733-2746.
[117] Coronado-Cáceres, L. J., Rabadán-Chávez, G., Mojica, L., Hernández-Ledesma, B., Quevedo-Corona, L., & Lugo Cervantes, E. (2020). Cocoa (Theobroma cacao l.) seed proteins' anti-obesity potential through lipase inhibition using in silico, in vitro and in vivo models. Foods, 9(10), 1359.
[118] Kim, M., Im, S., Cho, Y. K., Choi, C., Son, Y., Kwon, D., ... & Lee, Y. H. (2020). Anti-obesity effects of soybean embryo extract and enzymatically-modified isoquercitrin. Biomolecules, 10(10), 1394.
[119] Khateeb, S., Albalawi, A., & Alkhedaide, A. (2021). Regulatory effect of diosgenin on lipogenic genes expression in high-fat diet-induced obesity in mice. Saudi Journal of Biological Sciences, 28(1), 1026-1032.
[120] Jeevanandam, J., Barhoum, A., Chan, Y. S., Dufresne, A., & Danquah, M. K. (2018). Review on nanoparticles and nanostructured materials: history, sources, toxicity and regulations. Beilstein journal of nanotechnology, 9(1), 1050-1074.
[121] Yi, M. H., Simu, S. Y., Ahn, S., Aceituno, V. C., Wang, C., Mathiyalagan, R., ... & Yang, D. C. (2020). Anti-obesity effect of gold nanoparticles from Dendropanax morbifera Léveille by suppression of triglyceride synthesis and downregulation of PPARγ and CEBPα signaling pathways in 3T3-L1 mature adipocytes and HepG2 cells. Current Nanoscience, 16(2), 196-203.
[122] Lee, M. S., Jung, S., Shin, Y., Lee, S., Kim, C. T., Kim, I. H., & Kim, Y. (2017). Lipolytic efficacy of alginate double-layer nanoemulsion containing oleoresin capsicum in differentiated 3T3-L1 adipocytes. Food & nutrition research.
[123] Berger, E., Colosetti, P., Jalabert, A., Meugnier, E., Wiklander, O. P., Jouhet, J., ... & Rome, S. (2020). Use of nanovesicles from orange juice to reverse diet-induced gut modifications in diet-induced obese mice. Molecular Therapy-Methods & Clinical Development, 18, 880-892.
[124] Mukhopadhyay, P., Maity, S., Mandal, S., Chakraborti, A. S., Prajapati, A. K., & Kundu, P. P. (2018). Preparation, characterization and in vivo evaluation of pH sensitive, safe quercetin-succinylated chitosan-alginate core-shell-corona nanoparticle for diabetes treatment. Carbohydrate polymers, 182, 42-51.
[125] Lee, E. J., Hwang, J. S., Kang, E. S., Lee, S. B., Hur, J., Lee, W. J., ... & Seo, H. G. (2019). Nanoemulsions improve the efficacy of turmeric in palmitate-and high fat diet-induced cellular and animal models. Biomedicine & Pharmacotherapy, 110, 181-189.