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THE ROLE OF SOME PLANTS SECONDARY COMPOUNDS IN DECREASING OBESITY AND OBESITY-RELATED INFLAMMATION: A REVIEW.

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ABSTRACT

Obesity occurs when the adipose tissue and adipose mass grow dramatically with the aid of two mechanisms, adipocyte hyperplasia and hypertrophy. Obesity is caused by several factors including diet, inadequate physical activity, dysregulation of the genes and adipocytokines involved in the lipid metabolism. Obesity is associated with many serious medical complications and increase the risk of hypertension, renal disease, type 2 diabetes, coronary heart disease and certain cancers. The expansion of adipose tissue produces numerous bioactive substances known as adipocytokines or adipokines. These substances may contribute to various metabolic diseases through altered glucose, lipid homeostasis and inflammatory responses. It has been documented that the plasma concentration of inflammatory mediators, such as interleukin-6 and tumor necrosis factor-α, is increased in obesity and type 2 diabetes. The primary targets for preventing and treating obesity are a reduction of the overall amount of body fat, prevention of extra fat accumulation and eradication of side effects associated with chemically formulated anti-obesity drugs.Various pharmacological approaches have been proposed for weight loss and/or minimizing weight regain. Of these, many researchers have focused on medicinal plants due to their anti-obesity properties. For example, polyphenols have anti-oxidative, anti-inflammatory and neuroprotective effects signifying the natural defense properties of plant-based foods. Antioxidants in polyphenols control inflammation and lipid metabolism. Polyphenols may also play a role in ameliorating obesity. Not with standing the publication of some excellent reviews on anti-obesity agents, the current paper recapitulates the mechanisms of some natural bioactive phytochemicals or plant secondary compounds. These compounds have been identified for their ability to prevent chronic disorders.

KEYWORDS: ***Obesity, adipose tissue, adipocyte, inflammation, anti-obesity drug, plant secondary compound.***

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INTRODUCTION

In general, obesity refers to abnormal accumulation of fat associated with negative effects on health. There are currently no exact and reliable procedures to measure true body fat, although a quantitative approach has been found to be clinically acceptable. This approach involves anthropometric measurements such as the height and weight of the individuals[1]. Body composition is approximated by computing the body mass index (BMI) and the weight in kilograms (kg) divided by the square of height in meters (m^2). The results is then plotted on recognized BMI standard references. In differentiating the definitions of overweight and obesity, the International Obesity Task Force (IOTF) and the Center for Disease Control (CDC) use global growth developments charts as a reference[1]. BMI has a close relationship with the levels of body fat and total body fat[2]. The most common definition of overweight includes BMI that ranges from 25 to 30 kg/m^2, whereas those with BMI beyond 30 kg/m^2 are categorized as obese[3]. These are are further grouped into three classes (Table 1). Alternative definitions includes BMI ranging from 85th to 95th percentile (overweight) and above 95th percentile (obese), according to age and sex[4].

Table 1
World health organization classification of body weight[5].

Classification	BMI range- kg/m^2
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	≥25.00
Pro obese	25.00-29.99
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	≥40.00

CAUSES OF OBESITY

Accumulation of adipose tissue results from energy imbalance, wherein the consumption of energy exceeds its expenditure (Figure 1). Additional causes include genetics, physical inactivity, and lifestyles, certain health conditions and some medication side effects[6]. Different socioeconomic factors contribute to the growth of obesity both in adults and children. In recent decades, the Asia-Pacific area and most of its population have experienced significant financial development[7]. Such changes are accompanied by urbanization and changes in lifestyles, prompting an adjustment towards unhealthy diets and reduction in daily physical activity. Genetically, obesity phenotypes are related to over 600 separate factors, markers and chromosomal regions[8]. Also, inherited variation in weight gain between individuals is attributed to resting metabolic rate, thermic response to food, nutrient partitioning and energy expenditure associated with physical activity[9]. Poston and Foreyt[10] stated that western living features a toxic environment that advances unhealthy eating and activity patterns. Other potential factors affecting obesity include exposure to specific microorganisms, advanced maternal age, insufficient sleep, hormone disorders, pharmaceutical iatrogenesis, a decrease in the variability of ambient temperatures and intrauterine and intergenerational effects. This indicates that the problem is substantial and needs urgent attention. Hence, we should increase our comprehension of adipose tissue physiology and the pathogenesis of obesity.

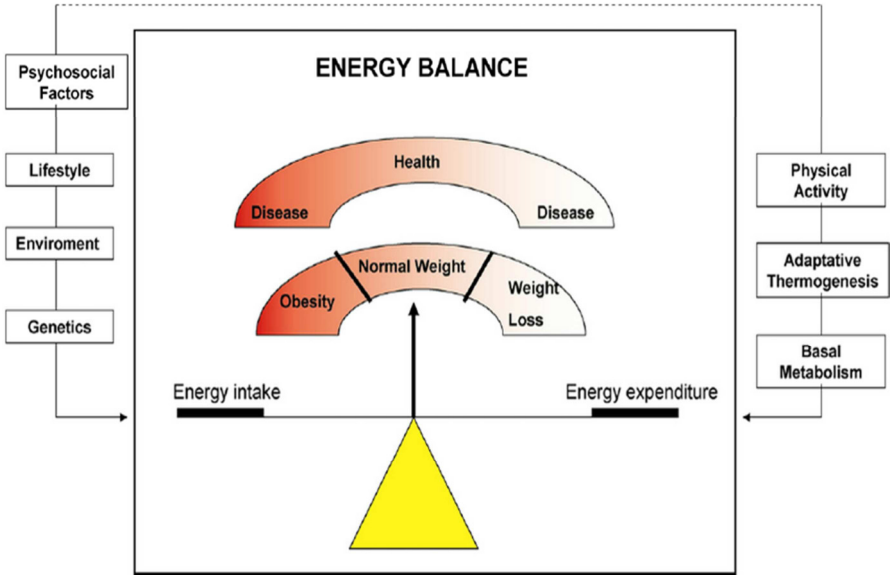
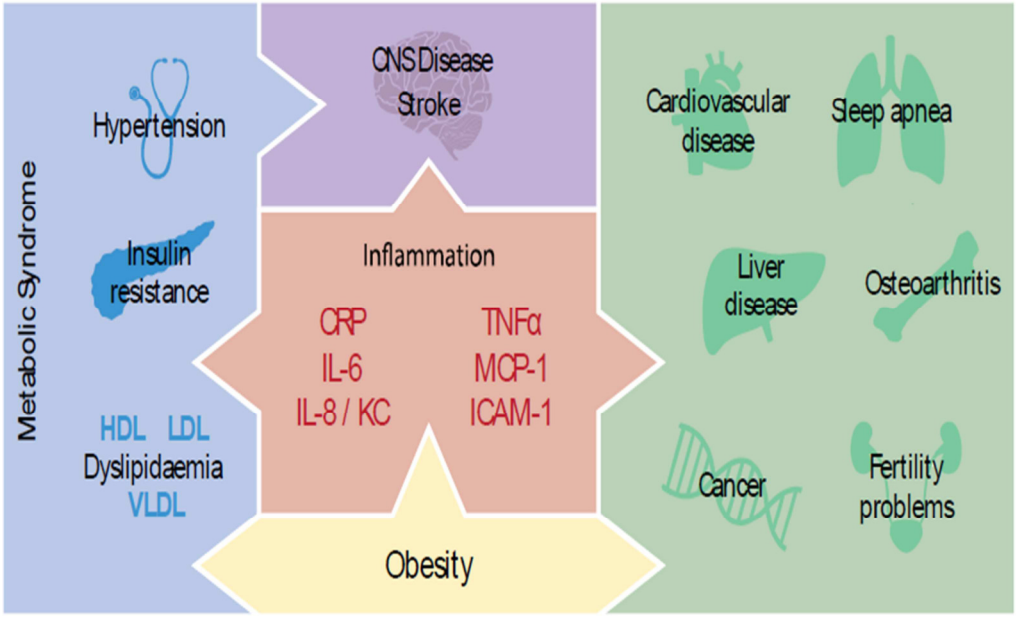


Figure 1
Fundamental principles of energy balance[11]

COMPLICATIONS OF OBESITY

The health implications of obesity are diverse, owing to the profound physiological changes that accompany adiposity. Figure 2 shows that Obesity results in a heightened risk of developing type-2 diabetes mellitus, coronary heart disease, hypertension, non-alcoholic fatty liver disease steatohepatitis, gastro-esophageal reflux, polycystic ovary syndrome (PCOS), infertility and certain types of cancer (Table 2)[13,14]. Furthermore, excess adipose tissue mass increases mechanical stress on the body, contributing to the development of respiratory complications (obstructive sleep apnea) and osteoarthritis musculoskeletal complications[15]. Regardless of this, the association between obesity and mortality is highly debatable for example, in recent years it is not only Western countries that have seen obesity rates increasing, but also developing countries have seen obesity rates rise as well .Furthermore, obesity rates going up throughout the globe, the problem is also affecting people of a younger age. For example, whilst obesity rates used to affect adults to a far greater extent than they did affect children, these days, obesity in childhood is becoming a far greater problematic , and could potentially pose a catastrophic health epidemic in years to come. However, according to Abdelaal *et al.,*[14] thirteen specific domains have been identified that account for morbidity and mortality in obesity. Cardiovascular disease (CVD) and cancer account for the greatest mortality risk associated with obesity. The association with overweight individuals and mortality remains doubtful[16]. Obesity should be considered an epidemic that threatens well-being, not just as a cosmetic phenomenon related only to some individuals but it is associated with medical complications that can shorten or reduce a person's quality of life. Flegal *et al.*,[17] proposed that relative to normal weight, Grades 2 and 3 obesity are associated with higher mortality whereas Grade 1 obesity was not. This suggests that mortality in obesity may be due to higher BMI levels.



CRP: C-reactive protein, IL-6: interleukin-6(humans), KC: keratinocyte chemoattractant (rodents), TNFα: tumor necrosis factor alpha, MCP1: monocyte chemo attractant protein-1, ICAM: intercellular adhesion molecule-1.

Figure 2
***Effects of obesity on health*[12].**

Table 2
***Cancers with a higher incidence reported in obese persons*[5].**

Hormone dependent	Gastrointestinal/ hepatic/ renal
Endometrial	Colorectal
Ovarian	Gallbladder
Breast	Pancreatic
Cervical	Liver
Prostate	Renal

ADIPOSE TISSUE

Adipose tissue (AT) can be defined as a loose connective tissue whose primary functions are energy storage, homeostasis, mechanical support, and insulation. AT is now recognized as an endocrine organ[18]. Adipose depots are crucial regulators of systemic metabolism. The two types of adipose depots found in humans are white adipose tissue (WAT) and brown adipose tissue (BAT) which are presented in Table 3.

Table 3
Difference between WAT and BAT[6].

	White adipose tissue	Brown adipose tissue
Functions	Energy storage	Increased energy expenditure
Morphology	Single lipid droplet The lower amount of mitochondria	Small droplets of lipid The higher amount of mitochondria
Characteristic uncoupling protein1 (UCP1)	No UCP1	Presence of UCP1
Human data	Associated with the accelerated risk of obesity and in health-related risk factors	It reduces the risk of obesity and health related risks
Impact of aging	Total body weight increased with aging	Reduces with age

LIPID STORAGE

Triglycerides (TG) are stored within the adipocytes of WAT and serve as a more efficient, but slowly accessible source of energy (Figure 3). Following consumption, dietary-derived TG arrives at the liver from the gut via the portal vein, or are released from the small intestine into the blood as chylomicrons[12]. During periods of excess energy, TG may be synthesized *de novo* in the liver, or directly within adipocytes[19]. This process is termed lipogenesis and is stimulated by insulin. This process involves the formation of new fatty acids (FA) from acetyl-CoA and malonyl-CoA precursors. The newly synthesized FAs are esterified with a molecule of glycerol-3-phosphate (G-3-P) to form triglycerides. From the liver, diet-derived or *de novo*-synthesized TGs are released into the blood as lipoproteins, mostly very-low-density lipoproteins (VLDL). TGs travelling in chylomicrons or other lipoproteins are hydrolyzed by lipoprotein lipase attached to the luminal surface of endothelial cells in the adipose tissue circulation. This releases FAs, which are taken up by specific FAs transporters into adipocytes. Adipocytes then re-esterify TGs from three FAs and one molecule of G-3-P, and store them intracellular in a lipid droplet.

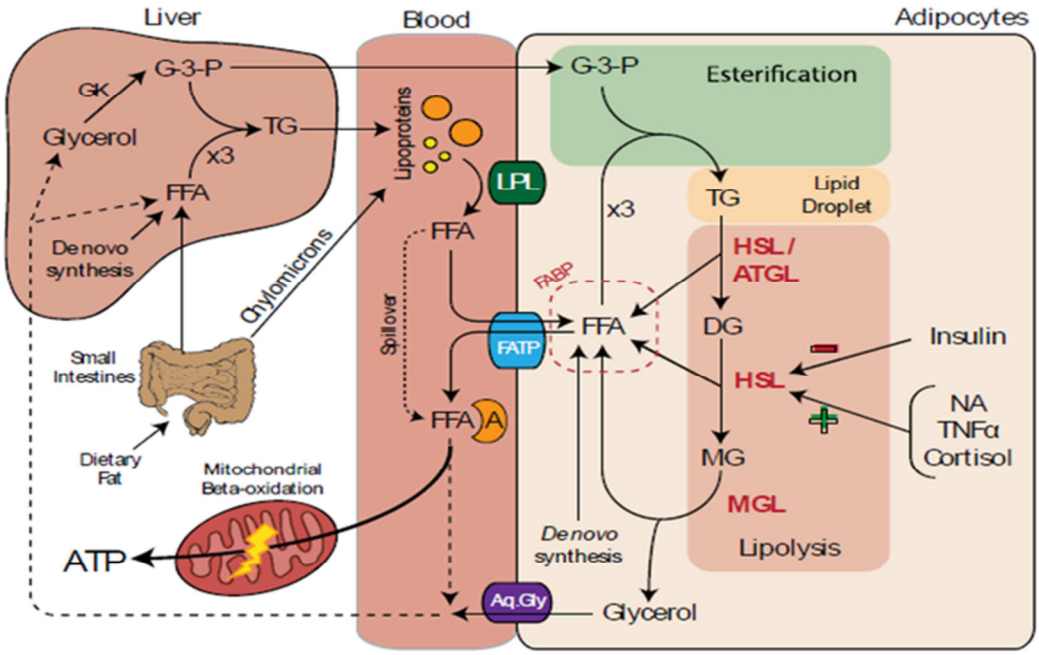


Figure 3
Lipid mobilization and storage[12]

MOBILIZATION OF LIPID STORES

Lipolysis of stored triglycerides causes the release of free fatty acids (FFA) into circulation. Lipolysis mostly occurs in adipocytes. The liver where TG are stored and is performed by a series of lipolytic enzymes. The lipolytic enzymes sequentially remove the three fatty acids (FA) chains from the glycerol backbone. The most well studied of these lipases is hormone-sensitive lipase (HSL). Hormone-sensitive lipase removes the first FA from TG to form a diacylglycerol (DG), which is the rate-limiting step in TG lipolysis and removes the second FA to form a monoacylglycerol (MG) (Figure 3). Hormone-sensitive lipase activity is increased by stimulation of β-adrenergic receptors on adipocytes by noradrenaline released by sympathetic nerve terminals and is inhibited by insulin[20]. The removal of the final FA from MG is catalyzed by MG lipase, though this is not a rate-limiting step. More recently, another lipase named adipose triglyceride lipase (ATGL) was also implicated. ATGL is also capable of removing the first FA from TG and controlling the rate of basal lipolysis. The complete hydrolysis of one TG thus liberates three FAs and one molecule of glycerol. However, lipolysis of TG does not always occur completely, intracellular MG and DG can

undergo re-esterification to form TGs for storage [12]. As adipose tissue lacks glycerol kinase (GK), glycerol must return to the liver via aquaglyceroporin channels (Aq.Gly) before glycerol-3-phosphate can be resynthesized [12]. Degradation of TGs involve major intracellular enzymes, including HSL and ATGL.

ADIPOSE CELLULARITY AND OBESITY

Adipose tissue consists of various cell types such as adipocytes, blood cells, adipose endothelial cells, precursor cells, fibroblasts, and monocytes/macrophage. The adipocytes are enclosed by a basement membrane, which consists of collagen IV, laminin and heparan sulfate proteoglycan. Consecutively, every adipocyte is in proximity to at least one capillary[21]. The reduction of the adipocyte diameter may differ from 10 to 150 µm in proportion. This droplet takes up nearly the whole cell cytoplasm, and the nuclei reject at the cell periphery. Moreno-Navarrete and Fernandez-Real[22] reported that numerous proteins are related to this structure and their roles in the integrity of the droplet, the alteration of its membrane and the management of their size. Figure 4, shows that once preadipocytes are activated to mature, they start to alter the -shape and go through a round of cell division referred to as clonal expansion. Following this, there is the initiation of the genetic programme that enables them to synthesize and store triglycerides[23]. Mature adipocytes are by and far the largest. Mature adipocytes can continue storing lipid when energy intake is more than the output, and their mobilization and oxidation of lipid is possible should energy expenditure exceed input[24]. Therefore, differentiation of preadipocytes to adipocytes depends on hormonal activity -and transcription factors[25]. The biologic procedures that result in obesity are described by an alteration in the properties of adipocytes cell, such as an increment in size (hypertrophy), number (hyperplasia) or both. The fat cell plasticity was described by Sethi and Vidal-Puig[26]. According to Gustafson *et al.*,[27] human adipocytes can modify about a thousand-fold in volume, twenty-fold in diameter, and become dysfunctional as adipocytes increase in size. Likewise, Rajala and Scherer[28] observed that smaller adipocytes are insulin-sensitive, whereas larger adipocytes are insulin-resistant and associated with the metabolic complication related to obesity.

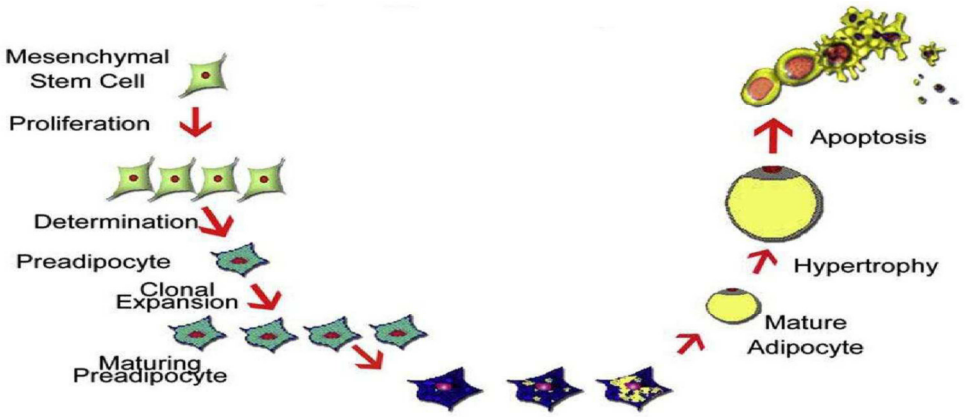


Figure 4
***Adipocyte cell cycle*[24]**

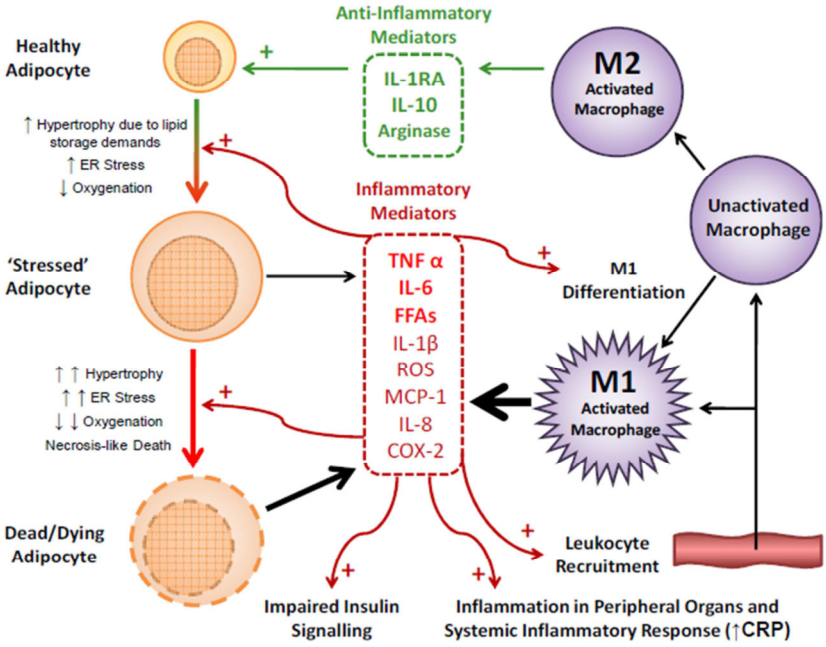
OBESITY AND INFLAMMATION

Obesity has a well-established association with disruption of pathways controlling lipid and glucose metabolism. However, recent evidence has shown that obesity also has an inflammatory component[12]. Inflammation is the term used to describe the environment produced by activated macrophages, including an environment of chemokine, cytokines, and other proteins that are a central aspect of the innate immune response. This response may be acute, as in the case of physical injury, infection, or low grade and chronic, as in long-term infections and autoimmune diseases[29]. Measures of obesity, such as BMI correlate with several markers of inflammation in patients. In particular, circulating concentrations of C-reactive protein (CRP), monocyte chemoattractant protein 1, tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), interleukin-8 (IL-8) and soluble intracellular adhesion molecule 1 (ICAM-1)[30]. This positive correlation between markers of inflammation and adiposity is due to suggestions that obesity is an inflammatory condition.

CHRONIC INFLAMMATION IN OBESITY

In WAT, constant nutritional excess outstrips the energy storage capacity of adipocytes. This physiological stress leads to inflammation in obesity[12]. Figure 5 shows normal adipose tissue function entails correct storage of lipids and appropriate release of adipokines, a state promoted by endogenous activated macrophages (M2). Obesity drastically increases the demand for lipid storage, forcing adipocytes to undergo hypertrophy to accommodate a growing lipid droplet. This hypertrophy leads to activation of cellular stress pathways within adipocytes. Metabolically stressed adipocytes then release pro-inflammatory mediators such as reactive oxygen species (ROS), cytokines and alter their adipokine signaling[31]. This disturbance in the redox state can affect tissues and promote further cell, DNA and protein damage through the production of peroxides and free radicals[32]. Adipocyte stress and inflammation may also be initiated by WAT hypoxia since the rapid expansion of WAT during obesity can lead to improper tissue oxygenation due to a lack of angiogenesis[33]. Endoplasmic reticulum (ER) stress may also occur in the adipose tissue in obesity, and triggers the unfolded protein response that results in activation of pro-

inflammatory and apoptotic pathways[31]. On the other hand, the crucial endocrine role of adipose tissue is evident in the growing family of WAT-derived protein factors, collectively known as adipokines[34]. Studies have identified over 50 adipokines, of which a small subset is described in Table 4.



M: Macrophage, IL-1RA: interleukin-1 receptor antagonist, ER: endoplasmic reticulum, TNFα: tumor necrosis factor alpha, ROS: reactive oxygen species, MCP1: monocyte chemo attractant protein-1, CO_x: cyclooxygenase-2.

Figure 5
Inflammation of adipose tissue due to obesity[17]

Table 4
Adipocyte-derived proteins with endocrine functions[35,36]

Cytokines and cytokine-related proteins	Leptin, TNFα, IL-6
Other immune-related proteins	monocyte chemo attractant protein-1 (MCP-1)
Proteins involved in the fibrinolytic system	Plasminogen activator inhibitor (PAI), tissue factor
Complement and complement-related proteins	Complement factor D (adipsin), complement factor B, adiponectin
Lipids and proteins for lipid metabolism or transport	Lipoprotein lipase (LPL), cholesterol ester transfer protein- (CETP), apolipoprotein E, nonesterified fatty acids (NEFAs).
Enzymes involved in steroid metabolism	Cytochrome, P450-dependent aromatase
Proteins of the acylating simulation protein	Angiotensinogen (AGT)
Other proteins	Resisten

ADIPOCYTOKINES

Adipokines are bioactive peptides that are produced by adipocytes[37]. Previously, little attention was given to adipose tissue as it was viewed as an organ for storing energy. More recently, adipose tissue is considered an endocrine organ as it produces several adipocytokines[36]. In 1987, adipsin or complement factor D was first considered as an adipocytokine and mainly derived from adipocytes[38].

LEPTIN

Leptin, which is produced exclusively by adipocytes, plays a vital role in nutrient intake modulation, energy expenditure and neuroendocrine function as well as regulating growth and reproduction[39]. The concentrations of leptin are directly related to the body fat. Following the discovery of leptin by Friedman and colleagues in 1994[40]. Its anorectic actions were made a target for anti-obesity treatment. In the central nervous system (CNS), leptin acts on hypothalamic neurons to reduce food intake and raise energy expenditure by promoting anorexigenic factors and preventing orexigenic neuropeptides[41]. It suppresses appetite that exerts its effects through interaction with a type 2 cytokine receptor in the hypothalamus, where it interacts with neuropeptide Y, melanocyte-stimulating hormone and the melanocortin-4 receptor[42]. When there is higher adiposity leptin plays a role in the peripheral lipid metabolism and insulin resistance in the pancreatic islets, adipose tissue, skeletal muscle and the liver[43]. Leptin facilitates the elevation of adenosine monophosphate kinase level which is associated with the induction of fatty acid oxidation[44]. This oxidation, in turn, reduces the damage of fatty acid entry into the mitochondria and improves acid oxidation through the activation of adenosine monophosphate kinase[44]. Despite all the functions mentioned above and even though the leptin function is suppressed, hyperleptinemia is evident in insulin resistance states in

obesity[45]. The effects of leptin on the immune system promote the inflammatory activation of macrophages, neutrophils and the release of pro-inflammatory cytokines[46]. Circulating leptin levels are usually elevated in obese patients, indicating a state of leptin resistance[34]. The changes in hypothalamus due to the elevated tumor necrosis factor (TNF)-alpha, IL-6 and IL10, the central action of leptin is impaired and lead to dysregulation of satiety[47]. Thus, it is possible that leptin plays a significant role in the inflammation changes linked to T2DM, atherosclerosis, and obesity[48].

TUMOUR NECROSIS FACTOR-A

TNFα is an adipocytokine which plays a major role in the progression of insulin resistance amongst cases seen with cancer and sepsis[49]. TNFα impairs insulin signaling by inhibiting the function of insulin receptor substrate 1 (IRS-1) through serine phosphorylation[50]. Neutralization of circulating TNFα enhances insulin sensitivity in insulin-resistant rodent models of diabetes and obesity[51] (Qatanani and Lazar, 2007). The role of TNFα in the insulin resistance of human T2DM and obesity is less clear. Circulating TNFα levels are increased in obese non-diabetic[52] and T2DM individuals [53]but the correlation between insulin resistance and plasma TNFα levels is weak in both obese and diabeticindividuals[53,54]. It should be emphasized, however, that TNFα exerts local paracrine effects, and the induction of insulin resistance may be more related to the local tissue TNFα concentration than to the levels in plasma. TNFα also is a potent inflammatory cytokine that has been implicated in the development of atherosclerosis in nonhuman models.[55]

INTERLEUKIN-6

Interleukin -6 (IL-6) an inflammatory cytokine, is clearly expressed in adipocytes[51]. IL-6 is a multifaceted, pleiotropic cytokine that plays a central role in the modulating of inflammation, hematopoiesis, immune responses and host defense mechanisms[48]. In rodent models of diabetes, adipokines have been shown to play a role in the development of insulin resistance in muscle and β-cell apoptosis[56]. In humans with type 2 diabetes mellitus, IL-6 levels are raised and associated with the sever condition of glucose intolerance[57]. In a chronic state, IL-6, which acts as a pro-inflammatory adipocytokine, contributes significantly to the lipid and carbohydrate metabolism, thus ultimately developing into a metabolic syndrome[33].

ADIPONECTIN

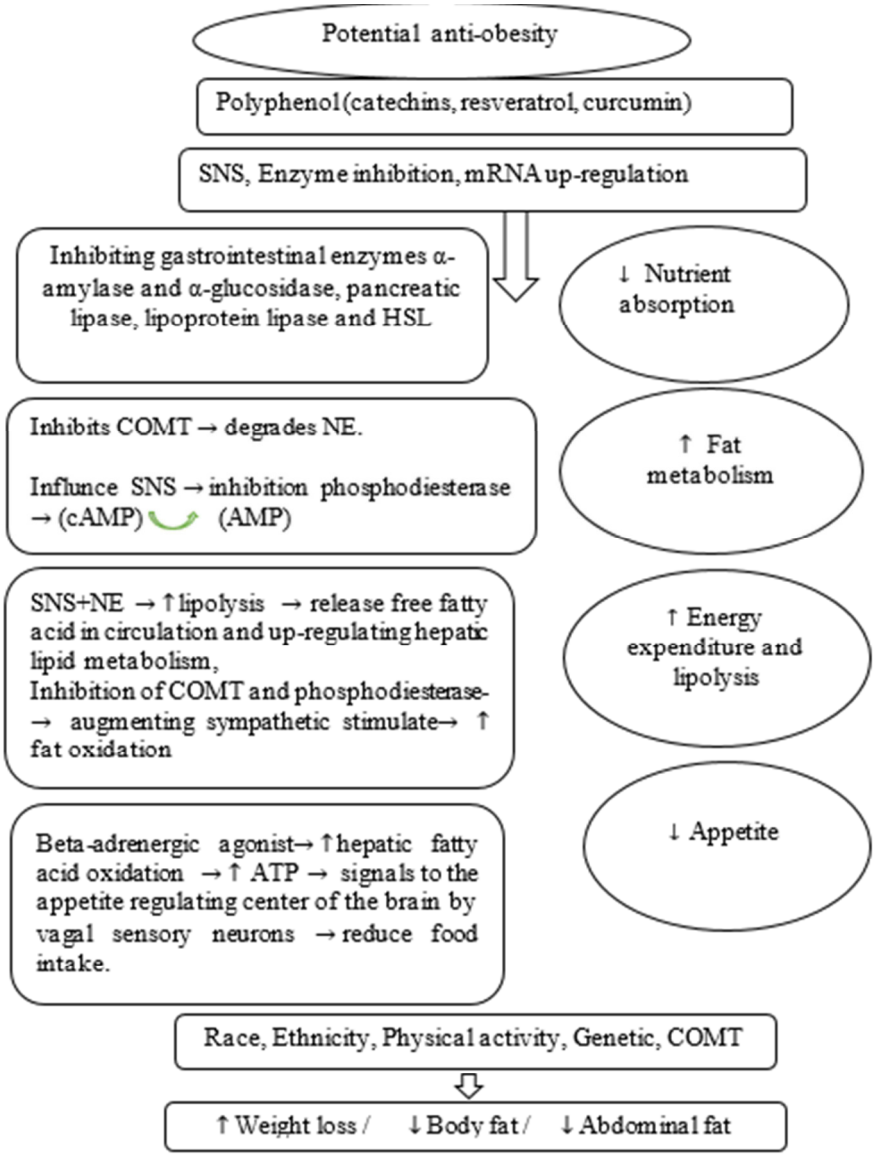
Adiponectin is one of the adipokines that play a role in the modulation of glucose metabolism, insulin resistance, and inflammation[58]. Recognized in 1995 as a novel protein produced mainly by adipocyte, adiponectin has been observed to circulate in increased concentrations in subjects with chronic heart failure[59]. Recent studies suggest that adiponectin is not only an adipocyte-specific endocrine molecule with cardioprotective effects, but it is also expressed in cardiomyocytes[60]. In addition, adiponectin has anti-diabetic and anti-inflammatory properties that include inhibition of TNF production in lipopolysaccharide-treated macrophages, reduction of TNF-induced monocyte adhesion, nuclear factor-B signaling, and expressions of intracellular adhesion molecule-1, endothelial cell adhesion molecule-1 and E-selectin in endothelial cells in vitro[61]. However, the biological significance of this locally produced adiponectin remains unclear. These effects could result from a change in adiponectin production or adiponectin clearance. Furthermore, it is also unclear which mechanisms result in the observed upregulation in circulating adiponectin levels of patients with advanced heart failure. Moreover, adiponectin has cardioprotective actions, and adiponectin receptors adipoR1 and adipo R2 mediate the suppressive effects of adiponectin on ET-1-induced hypertrophy in cultured cardiomyocytes[62].

PLANTS FOR TREATING OBESITY

The study of obesity treatments first gained popularity in the mid-19th century when industrialization-led obesity emerged as a predominant issue[63]. Vinegar was widely touted as obesity therapy similar to descendants such as pineapple, grapefruit and cabbage soup and continued to be much used with each new generation of dieters[63]. Mermel[63] suggest that the reason behind the utilization of this food is their acidic makeup and enzyme content truly rate up fat. Similarly, Warwick and Schiffman[64] reported that several herbal supplements like *Allium sativum* L., *Citrus aurantium* L., *Cyperus Rotundus* L., *Glycyrrhiza glabra* Linn, are useful for treating obesity and its related diseases. Amongst those used for their anti-obesity effect is the *Irvingia gabonensis* leaves extract[65]. Additionally, the anti-obesity potential of *Moringa oleifera* in rats has also been demonstrated[66]. Numerous other herbal medications have also shown promising anti-obesity and hypolipidemic properties. These include black Chinese tea aqueous extract[67], fenugreek seeds *Trigonella foenum-graecum* L extract[68] oolong tea[69] amongst others. Wadden[70] stated that diet manufacturing had paid attention to the continuing maintenance of weight loss in obese patients. Many patients prefer slimming products and drugs for weight loss compared to physical activities and change in their dietary habits. However, some anti-obesity drugs have dangerous side-effects as shown in Table 5[71]. Consequently, anti-obesity drugs constituted up to 6% of overall healthcare costs in several developed countries[72]. Besides this, active constituents of herbs or medicinal plants were also found to be capable of controlling obesity and its complications[73]. Ranjbar *et al.*,[74] revealed the importance of the using different medicinal plants and their extracts for preventing diet-induced obesity and induce weight loss. Herbal products are the safe options for those who want to lose weight naturally[75].

Table 5
Some common anti-obesity drugs with mode of action and side effects[71].

Drugs	Mechanism of action	Side effects
Phentermine (Fastin) Diethylpropion	Appetite suppressant reduces food intake. Sympathomimetic amine causes release of norepinephrine by the cells.	Headache, insomnia, irritability, palpitation and nervousness
Fluoxetine (Prozac)	Reduces food intake through selective inhibition of serotonin re-uptake.	Agitation and nervousness
Sibutramine (Meridia)	Reduces food intake through combined norepinephrine and serotonin re-uptake inhibition (Neurochemical actions).	Headache, insomnia, dry mouth and constipation, long term treatment increases the risk of heart attack and stroke
Orlistat (Xenical)	Lipase inhibitor reduces fat absorption (Gastrointestinal tract actions).	Diarrhea, flatulence, bloating, abdominal pain, and dyspepsia
Rimonabant (Acomplia)	Selective CB1 receptor blocker reduces food intake.	Nausea, dizziness, arthralgia, and diarrhea



SNS: Sympathetic nervous system, NE: nor epinephrine, cAMP: cyclic adenosine monophosphate, COMT: catechol methyl transferase, HSL: Hormone-sensitive lipase, mRNA: messenger ribonucleic acid.

Figure 6
The Anti-obesity roles of plant secondary compound[79].

THE ANTI-OBESITY ROLES OF PLANT SECONDARY COMPOUNDS

Dietary polyphenols are integral in dealing with obesity because its components, such as curcumin, anthocyanins, catechin and resveratrol are capable of adjusting molecular and physiological pathways in adiposity and energy metabolism. Recent emerging studies have investigated the effects of plant secondary

compounds in response to obesity and the function of polyphenols in body weight management[76]. Ahn *et al*.,[77] and Zhao *et al*.,[78] showed that epigallocatechin gallate (EGCG), resveratrol and curcumin have anti-obesity characteristics. These include the inhibition of differentiation of adipocyte and proliferation, hindrance of absorption of fat from the gut, and inhibition of catechol-o-methyl transferase (COMT), an enzyme that reduces oxidation of fatty acid and response of inflammatory in adipose tissue as shown in Figure 6[79] Polyphenol hinders several lipases such as pancreatic and lipoprotein lipases. However, lipoprotein lipase hydrolyzes the triacylglycerols of low-thickness lipoproteins and chylomicrons, hence discharging free fatty acids for take-up into adipocytes[80]. Therefore, the hindrance of HSL can possibly decrease the levels of coursing free fatty acids connected to insulin resistance in obese patients[81]. Green tea catechins may have the ability to change the lipid metabolism by stimulating lipolysis especially in the abdominal fat depot as changes in the fatty acid metabolism specifically reduces abdominal adiposity as compared to other areas of fat accumulation[82]. Green tea epicatechin enhances fecal production of cholesterol primarily due to its ability to bind and hasten cholesterol discharge. In fact, green tea epicatechins may reduce the absorption of cholesterol by forming insoluble coprecipitates of cholesterol and reducing bile acid-induced micellar solubility[83]. In line with the current observation, plant secondary metabolites, including chlorogenic acid[84], trans-resveratrol[85],epicatchin[86]and dietary fiber from cocoa[87] inhibited lipid peroxidation[86]. Fernandez-Mar *et al*.,[88] reported that at least 70% of ingested trans-resveratrol was absorbed and metabolized to form glucuronide and sulfate derivatives, which suppress pathological increases in lipid peroxidation. As recently highlighted by de Melo *et al*.,[89] showed that oleanolic acid a natural triterpenoid when administered daily (50 mg/L in drinking water), to high fat diet (HFD) fed adult male Swiss mice for 15 weeks, after which they confirmed that the oleanolic acid and triterpene had been decreased the IL-6 production. Supplementation of Blueberry juice or purified blueberry anthocyanins (1.0 mg/mL) in the drinking water were fed male C57BL/6J mice for a period of 72 days[90] and anthocyanin-rich grape- bilberry juice[91] decreased serum leptin levels in mice fed HFD. Hence, there is a great need to explore the anti-obesity activity of different plant/ herbal extracts.

CONCLUSION

Adipose tissues (AT) are loose connective tissues whose primary functions are energy storage, homeostasis, mechanical support and insulation. Some of the polyphenol metabolites are capable of modulating molecular and physiological pathways to prevent the development of adiposity. However, different studies on the management of obesity and overweight gain have not been fruitful due to the phenomenon of rapid weight regain. Behavioral change, diet change and increased physical modification are the most successful elements in weight loss. Weight loss surgery is the most effective and long-lasting solution for obesity. Obesity deserves significant attention and can be prevented through increased physical activity and dietary improvement. An excellent example of improved dietary choice is the inclusion of five to six portions of fruits and veggies daily.

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AUTHOR CONTRIBUTION STATEMENT

All the authors take responsibility for the entire content of the submitted manuscript.

CONFLICT OF INTEREST

Conflict of interest declared none.

REFERENCES

1. Partap U, Young EH, Allotey P, Sandhu MS, Reidpath DD. The Use of Different International References to Assess Child Anthropometric Status in a Malaysian population. J Pediatr. 2017;190:63-8. DOI: https://doi.org/10.1016/j.jpeds.2017.07.049
2. Andersen RE, Crespo CJ, Bartlett SJ, Cheskin LJ, Pratt M. Relationship of physical activity and television watching with body weight and level of fatness among children: results from the Third National Health and Nutrition Examination Survey. JAMA. 1998 March 25;279(12):938-42. DOI:https://doi:10.1001/jama.279.12.938
3. World Health Organization [Internet]. World Health Organization obesity and overweight fact sheet. WHO; 2017 [cited 2017 Oct 18]. Available from: http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
4. Skinner AC, Skelton JA. Prevalence and trends in obesity and severe obesity among children in the United States, 1999-2012. JAMA Pediatr. 2014 Jun1;168(6):561-6. DOI: https://doi:10.1001/jamapediatrics.2014.21
5. World Health Organization. Obesity, preventing and managing the global epidemic. Technical Report Series 894. Geneva: Switzerland; 2000. 5-77.p. Available from: http://www.who.int/nutrition/publications/obesity/WHO_TRS_894/en/
6. Otieno D. Effects of Beetroot Extract in Brown Adipose Tissue from Diet-induced Obese Mice (Doctoral dissertation, North Carolina Agricultural and Technical State University),USA: 2016.
7. Goh LY, Goh KL. Obesity: an epidemiological perspective from Asia and its relationship to gastrointestinal and liver cancers. J Gastroenterol Hepatol. 2013 Dec 1;28(S4):54-8. DOI: 10.1111/jgh.12293.
8. Xiao Q, Wu XL, Michal JJ, Reeves JJ, Busboom JR, Thorgaard GH, Jiang Z. A novel nuclear-encoded mitochondrial poly (A) polymerase

PAPD1 is a potential candidate gene for the extreme obesity related phenotypes in mammals. Int J Biol Sci. 2006 May 18;2(4):171. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1483122/

9. Weinsier RL, Hunter GR, Heini AF, Goran MI, Sell SM. The etiology of obesity: relative contribution of metabolic factors, diet, and physical activity. Am J Med. 1998 Aug 1;105(2):145-50. DOI: https://doi.org/10.1016/S0002-9343(98)00190-9
10. Poston WS, Foreyt JP. Obesity is an environmental issue. Atheroscler. 1999 Oct 1;146(2):201-9. DOI: https://doi.org/10.1016/S0021-9150(99)00258-0
11. Prieto-Hontoria PL, Pérez-Matute P, Fernández-Galilea M, Bustos M, Martínez JA, Moreno-Aliaga MJ. Role of obesity-associated dysfunctional adipose tissue in cancer: a molecular nutrition approach. Biochimica et Biophysica Acta (BBA)-Bioenergetics. 2011 Jun 1;1807(6):664-78. DOI: https://doi.org/10.1016/j.bbabio.2010.11.004
12. Haley M. Mechanisms of interaction between obesity and ischaemic stroke (Doctoral dissertation, University of Manchester), UK; 2014.
13. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. JAMA. 1999 Oct 27;282(16):1523-9. DOI: 10.1001/jama.282.16.1523
14. Abdelaal M, le Roux CW, Docherty NG. Morbidity and mortality associated with obesity. Ann Transl Med. 2017 Apr; 5(7):161. DOI: 10.21037/atm.2017.03.107
15. Kopelman PG. Obesity as a medical problem. Nature. 2000 Apr 6;404(6778):635-43. Available from: https://www.nature.com/articles/35007508
16. González-Castejón M, Rodriguez-Casado A. Dietary phytochemicals and their potential effects on obesity: a review. Pharmacol Res. 2011 Nov 1;64(5):438-55. DOI: https://doi.org/10.1016/j.phrs.2011.07.004
17. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA. 2013 Jan 2;309(1):71-82. DOI: 10.1001/jama.2012.113905
18. Householder LA. Examining the Impact of Growth Hormone on the Collagen Content of Adipose Tissue in Transgenic Mice (Doctoral dissertation, Ohio University), USA; 2013. Available from: https://etd.ohiolink.edu/!etd.send_file?accession=ohiou1376475963&disposition=inline
19. Foufelle F, Ferre P. Mechanism of storage and synthesis of fatty acids and triglycerides in white adipocytes. In: Bastard J, Feve B, editors, Physiology and physiopathology of adipose tissue. Parise: Springer; 2013.101-21.p
20. Kraemer FB. Shen WJ. Hormone-sensitive lipase control of intracellular tri-(di-) acylglycerol and cholesteryl ester hydrolysis. J Lipid Res. 2002 Oct 1;43(10):1585-94. DOI: 10.1194/jlr.R200009-JLR200
21. Pierleoni C, Verdenelli F, Castellucci M, Cinti, S. Fibronectins and basal lamina molecules expression in human subcutaneous white adipose tissue. Eur J Histochem.1998 Jan 1;42(3):183-8. Available from: https://europepmc.org/abstract/med/9857243
22. Moreno-Navarrete JM, Fernandez-Real JM. Adipocyte differentiation. In: Adipose tissue biology. Springer, Cham; 2017. 69-90.p
23. Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. Cell. 2001 Feb 23;104(4):531-43. DOI: https://doi.org/10.1016/S0092-8674(01)00240-9
24. Rayalam S, Della-Fera MA, Baile CA. Phytochemicals and regulation of the adipocyte life cycle. J Nutr Biochem. 2008 Nov 1;19(11):717-26. DOI: 10.1016/j.jnutbio.2007.12.007.
25. Farmer SR. Transcriptional control of adipocyte formation. Cell Metab. 2006 Oct 1;4(4):263-73. DOI: https://doi.org/10.1016/j.cmet.2006.07.001
26. Sethi JK, Vidal-Puig AJ. Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation. J Lipid Res. 2007 Jun 1;48(6):1253-62. Available from: http://www.jlr.org/content/48/6/1253.full.pdf
27. Gustafson B, Hammarstedt A, Andersson CX, Smith U. Inflamed adipose tissue a culprit underlying the metabolic syndrome and atherosclerosis. Arterioscler Thromb Vasc Biol. 2007 Nov 1;27(11):2276-83. Available from: https://www.ahajournals.org/doi/abs/10.1161/ATVBAHA.107.147835.
28. Rajala MW, Scherer PE. Mini review: the adipocyte-at the crossroads of energy homeostasis, inflammation and atherosclerosis. Endocrinol. 2003 Sep 1;144(9):3765-73. DOI: https://doi.org/10.1210/en.2003-0580
29. Bruunsgaard, H. Physical activity and modulation of systemic low-level inflammation. J Leukoc Biol [Internet]. 2005 Oct 1;78(4):819-35. DOI: https://doi.org/10.1189/jlb.0505247
30. Thompson AM, Zhang Y, Tong W, Xu T, Chen J, Zhao L, He J. Association of obesity and biomarkers of inflammation and endothelial dysfunction in adults in Inner Mongolia, China. Int J Cardiol. 2011 Aug 4;150(3): 247-52. DOI: https://doi.org/10.1016/j.ijcard.2010.04.011
31. Hummasti S, Hotamisligil GS (2010). Endoplasmic reticulum stress and inflammation in obesity and diabetes. Circ Res. 2010 Sep 3;107(5):579–91. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.922.3817&rep=rep1&type=pdf
32. Guzik T, Korbut R, Adamek-Guzik T. Nitric oxide and superoxide in inflammation. J Physiol Pharmacol. 2003; 54(4):469-87.
33. Fain JN. Release of inflammatory mediators by human adipose tissue is enhanced in obesity and primarily by the nonfat cells: a review. Mediators Inflamm. 2010;1-20. DOI: http://dx.doi.org/10.1155/2010/513948
34. Black CL. A Role for Central Leptin Signaling in Maintaining Myocardial Fatty Acid Oxidation (Doctoral dissertation, Department of Biochemistry, University of Utah).USA; 2010.

35. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metabo. 2004 Jun 1;89(6): 2548-56.
DOI: https://doi.org/10.1210/jc.2004-0395
36. Ouchi N, Ohashii K, Shibata R, Murohara T. Adipocytokines and obesity-linked disorders. Nagoya J Med Sci. 2012 Feb ;74(1-2):19-30. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4831247/
37. Chaldakov GN, Stankulov IS, Hristova M, Ghenev PI. Adipobiology of disease: adipokines and adipokine-targeted pharmacology. Curr Pharm Des. 2003 May 1;9(12):1023-1031.
DOI: https://doi.org/10.2174/1381612033455152.
38. Cook KS, Min HY, Johnson D, Chaplinsky RJ, Flier JS, Hunt CR, Spiegelman BM. Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve Sci. 1987 Jul 24;237(4813):402-5.
DOI: 10.1126/science.3299705.
39. Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Müller C, Carling D, Kahn BB. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature 2002 Jan;415(6869):339-43. Available from: https://www.nature.com/articles/415339a
40. Rohner-Jeanrenaud F, Jeanrenaud B. The discovery of leptin and its impact in the understanding of obesity. Eur J Endocrinol.1996 Dec 1;135(6):649-50.
DOI: https://doi.org/10.1530/eje.0.1350649
41. Lago F, Gomez R, Gomez-Reino JJ, Dieguez C, Gualillo O. Adipokines as novel modulators of lipid metabolism. Trends Biochem Sci. 2009 Oct 1;34(10):500-10.
DOI: https://doi:10.1016/j.tibs.2009.06.008
42. Zhou Y, Rui L. Leptin signaling and leptin resistance. Front Medic. 2013 Jun 1;7(2):207-22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4069066/
43. Morris DL, Rui L. Recent advances in understanding leptin signaling and leptin resistance. Am J Physiol-Endocrinol Metabo. 2009 Sep 1; 297(6):1247-59.
DOI: 10.1152/ajpendo.00274.2009.
44. Guerrero-Berroa E, Schmeidler J, Beeri MS. Neuropathology of type 2 diabetes: a short review on insulin-related mechanisms. Eur Neuropsychopharmacol. 2014 Dec 1;24(12):1961-6. DOI: https://doi.org/10.1016/j.euroneuro.2014.01.019
45. Lustig RH, Mietus-Snyder ML, Bacchetti P, Lazar AA, Velasquez-Mieyer PA, Christensen, ML. Insulin dynamics predict body mass index and z-score response to insulin suppression or sensitization pharmacotherapy in obese children. J Pediatr. 2006;148(1):23-9.
DOI: https://doi.org/10.1016/j.jpeds.2005.08.075.
46. Fernondez-Riejos P, Najib S, Santos-Alvarez J, Martin-Romero C, Perez-Perez A, Gonzalez-Yanes C, Sanchez-Margaletm V. Role of leptin in the activation of immune cells. Mediators Inflam. 2010; Article ID 568343.
DOI: http://dx.doi.org/10.1155/2010/568343
47. van de Sande-Lee S, Pereira FR, Cintra DE, Fernandes PT, Cardoso AR, Garlipp CR, Li L M. Partial reversibility of hypothalamic dysfunction and changes in brain activity after body mass reduction in obese subjects. Diabetes. 2011 Jan 1;60(6):1699-1704.
DOI: https://doi.org/10.2337/db10-1614
48. Makki K, Froguel P, Wolowczuk I. Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. ISRN Inflamm. 2013 Dec 22;1-12. Article ID: 139239.
DOI: http://dx.doi.org/10.1155/2013/139239.
49. Mohd-Radzman NH, Ismail WI, Adam Z, Jaapar SS, Adam A. Potential roles of Stevia rebaudiana Bertoni in abrogating insulin resistance and diabetes: a review. Evidence-Based Complementary and Alternative Medicine. 2013;2013. Article ID: 718049.
DOI: http://dx.doi.org/10.1155/2013/718049
50. Parola M, Marra F. Adipokines and redox signaling: impact on fatty liver disease. Antioxidants & redox signaling. 2011 Jul 15;15(2):461-83.
DOI: https://doi.org/10.1089/ars.2010.3848.
51. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. Genes & Develop. 2007 Jun 15;21(12):1443-55. Available from: http://www.genesdev.org/cgi/doi/10.1101/gad.1550907.
52. Inadera H. The usefulness of circulating adipokine levels for the assessment of obesity-related health problems. Int J Med Sci. 2008 Aug 29;5(5):248-62. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2528071/
53. Miyazaki Y, Pipek R, Mandarino LJ, DeFronzo RA. Tumor necrosis factor α and insulin resistance in obese type 2 diabetic patients. Int J Obes Related. 2003 Jan;27(1):88-94. Available from: https://www.nature.com/articles/0802187
54. Zinman B, Hanley AJ, Harris SB, Kwan J, Fantus IG. Circulating tumor necrosis factor-α concentrations in a native Canadian population with high rates of type 2 diabetes mellitus. J Clin Endocrinol Metab. 1999 Jan 1; 84(1): 272-8. https://doi.org/10.1210/jcem.84.1.5405.
55. Autieri MV. Pro-and anti-inflammatory cytokine networks in atherosclerosis. ISRN Vascular Medicine. 2012 Nov 19;2012:1-17.
DOI: 10.5402/2012/987629
56. Wei Y, Chen K, Adam I, Whaley-Connell AT, Stump CS, Ibdah JA, Sowers JR. Skeletal muscle insulin resistance: role of inflammatory cytokines and reactive oxygen species. Am J Physiol Regul Integr Comp Physiol. 2008 Mar;294(3):673-80. DOI: https://doi.org/10.1152/ajpregu.00561.2007
57. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA. 2001 Jul 18; 286(3):327-34. DOI: 10.1001/jama.286.3.327.
58. Tang CH, Chiu YC, Tan TW, Yang RS, Fu WM. Adiponectin enhances IL-6 production in human synovial fibroblast via an AdipoR1 receptor,

AMPK, P38 and NF-kB pathway. J Immunol. 2007 Oct 15;179 (8):5483-5492.
DOI: https://doi.org/10.4049/jimmunol.179.8.5483
59. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, Hildebrandt P. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation. 2005 Sep 20;112(12):1756–62. Available from: 10.1161/CIRCULATIONAHA.104.530972
60. Wang Y, Lau WB, Gao E, Tao L, Yuan Y, Li R, Ma XL. Cardiomyocyte-derived adiponectin is biologically active in protecting against myocardial ischemia-reperfusion injury. Am J Physiol Endocrinol Metab. 2010 Dec 22; 298(3):E663–E670.
DOI: https://doi.org/10.1152/ajpendo.00663.2009.
61. Spranger J, Kroke A, Möhlig M, Bergmann MM, Ristow M, Boeing H, Pfeiffer AF. Adiponectin and protection against type 2 diabetes mellitus. The Lancet. 2003 Jan 18;361(9353):226-8. DOI: https://doi.org/10.1016/S0140-6736(03)12255-6
62. Yin WH, Chen YH, Wei J, Jen HL, Huang WP, Young MS, Liu PL.. Associations between endothelin-1 and adiponectin in chronic heart failure. Cardiol. 2011;118(4):207–16.
DOI: https://doi.org/10.1159/000328780
63. Mermel VL. Old paths new directions: the use of functional foods in the treatment of obesity. Trends Food Sci Technol. 2004 Nov 1;15(11):532-40. Available from: https://doi.org/10.1016/j.tifs.2004.03.0054.
64. Warwick ZS, Schiffman SS. Role of dietary fat in calorie intake and weight gain. Neurosci Biobehav Rev. 1992 Jan 1;16(4):585-96. DOI: https://doi.org/10.1016/S0149-7634(05)80198-8.
65. Ngondi JL, Etoundi BC, Nyangono CB, Mbofung CM, Oben JE. IGOB131, a novel seed extract of the West African plant Irvingia gabonensis, significantly reduces body weight and improves metabolic parameters in overweight humans in a randomized double-blind placebo controlled investigation. Lipids Health Dis. 2009 Dec; 8(1):7. DOI: https://doi.org/10.1186/1476-511X-8-7.
66. Bais S, Singh GS, Sharma R. Antiobesity and hypolipidemic activity of Moringa oleifera leaves against high fat diet-induced obesity in rats. Adv Biol. 2014. Article ID: 162914. DOI: http://dx.doi.org/10.1155/2014/162914
67. Kubota K, Sumi S, Tojo H, Sumi-Inoue Y, Hou I, Oi Y, Fujita H, Urata H. Improvements of mean body mass index and body weight in preobese and overweight Japanese adults with black Chinese tea (Pu-Erh) water extract. Nutr Res. 2011 Jun 1; 31(6):421-8.
DOI: https://doi.org/10.1016/j.nutres.2011.05.004
68. Chevassus H, Gaillard JB, Farret A, Costa F, Gabillaud I, Mas E, Dupuy AM, Michel F, Cantié C, Renard E, Galtier F. A fenugreek seed extract selectively reduces spontaneous fat intake in overweight subjects. Eur J Clin Pharmacol. 2010 May 1;66(5):449-55. Available from: https://link.springer.com/article/10.1007/s00228-009-0770-0
69. He RR, Chen L, Lin BH, Matsui Y, Yao XS, Kurihara H. Beneficial effects of oolong tea consumption on diet-induced overweight and obese subjects. Chin J Integr Med. 2009 Feb 1;15(1):34-41. Available from: https://link.springer.com/article/10.1007/s11655-009-0034-8
70. Wadden TA. Treatment of obesity by moderate and severe caloric restriction: results of clinical research trials. Ann Intern Med. 1993 Oct 1;119(7_2):688-93.DOI: 10.7326/0003-4819-119-7_Part_2-199310011-00012.
71. Mohamed GA, Ibrahim SR, Elkhayat ES, El Dine RS. Natural anti-obesity agents. Bulletin of Faculty of Pharmacy, Cairo University. 2014 Dec 1;52(2):269-84.
DOI: https://doi.org/10.1016/j.bfopcu.2014.05.001.
72. Birari RB, Bhutani KK. Pancreatic lipase inhibitors from natural sources: unexplored potential. Drug Discovery Today. 2007 Oct 1;12(19-20):879-89.
DOI: https://doi.org/10.1016/j.drudis.2007.07.024
73. Lenon GB, Li KX, Chang YH, Yang AW, Da Costa C, Li CG, Cohen M, Mann N, Xue CC. Efficacy and safety of a Chinese herbal medicine formula (RCM-104) in the management of simple obesity: a randomized, placebo-controlled clinical trial. J Evid Based Complementary Altern Med. 2012; 2012. Article ID:435702.
DOI: http://dx.doi.org/10.1155/2012/435702
74. Hasani-Ranjbar S, Nayebi N, Moradi L, Mehri A, Larijani B, Abdollahi M. The efficacy and safety of herbal medicines used in the treatment of hyperlipidemia; a systematic review. Curr Pharm Des. 2010 Sep 1; 16(26):2935-47. DOI:https://doi.org/10.2174/138161210793176464.
75. Kazemipoor M, Cordell GA, Sarker MM, Radzi CW, Hajifaraji M, En Kiat P. Alternative treatments for weight loss: safety/risks and effectiveness of anti-obesity medicinal plants. Int J Food Prop. 2015 Sep 2;18(9):1942-63. DOI: https://doi.org/10.1080/10942912.2014.933350
76. Meydani M, Hasan ST. Dietary polyphenols and obesity. Nutrients. 2010 Jul 8;2(7):737-51.
DOI: 10.3390/nu2070737.
77. Ahn J, Lee H, Kim S, Ha T. Curcumin-induced suppression of adipogenic differentiation is accompanied by activation of Wnt/β-catenin signaling. Am J Physiol Cell Physiol. 2010 Mar 31;298(6):C1510-6.
DOI: https://doi.org/10.1152/ajpcell.00369.2009.
78. Zhao J, Sun XB, Ye F, Tian WX. Suppression of fatty acid synthase, differentiation and lipid accumulation in adipocytes by curcumin. Mol Cell Biochem. 2011 May 1;351(1-2):19-28. Available from: https://link.springer.com/article/10.1007/s11010-010-0707-z
79. Hursel R, Westerterp-Plantenga MS. Thermogenic ingredients and body weight regulation. Int J Obes. 2010 Apr;34(4):659. Available from: https://www.nature.com/articles/ijo2009299
80. Wong H, Schotz MC. The lipase gene family. J Lipid Res. 2002 Jul 1;43(7):993-9.
DOI: 10.1194/jlr.R200007-JLR200.
81. Moreno DA, Ilic N, Poulev A, Brasaemle DL, Fried SK, Raskin I. Inhibitory effects of grape seed extract on lipases. Nutrition. 2003 Oct

1;19(10):876-9. DOI: https://doi.org/10.1016/S0899-9007(03)00167-9

82. Rains, T.M., Agarwal, S. and Maki, K.C. Antiobesity effects of green tea catechins: a mechanistic review. J Nutr biochem. 2011;22(1):1-7. DOI: https://doi.org/10.1016/j.jnutbio.2010.06.006.
83. Chan PT, Fong WP, Cheung YL, Huang Y, Ho WK, Chen ZY. Jasmine green tea epicatechins are hypolipidemic in hamsters (*Mesocricetus auratus*) fed a high fat diet. J Nutr. 1999 Jun 1;129(6):1094-101. DOI: https://doi.org/10.1093/jn/129.6.1094
84. Kono Y, Kobayashi K, Tagawa S, Adachi K, Ueda A, Sawa Y, Shibata H. Antioxidant activity of polyphenolics in diets: rate constants of reactions of chlorogenic acid and caffeic acid with reactive species of oxygen and nitrogen. Biochim Biophys Acta. 1997 Jun 6;1335(3):335-42. DOI: https://doi.org/10.1016/S0304-4165(96)00151-1.
85. Macedo LF, Rogero MM, Guimarães JP, Granato D, Lobato LP, Castro IA. Effect of red wines with different in vitro antioxidant activity on oxidative stress of high-fat diet rats. Food chem. 2013 Apr 15;137(1-4):122-9. DOI: https://doi.org/10.1016/j.foodchem.2012.10.017.
86. Baba S, Natsume M, Yasuda A, Nakamura Y, Tamura T, Osakabe N, Kanegae M, Kondo K. Plasma LDL and HDL cholesterol and oxidized LDL concentrations are altered in normo-and hypercholesterolemic humans after intake of different levels of cocoa powder. J Nutr. 2007 Jun 1;137(6):1436-41. DOI: https://doi.org/10.1093/jn/137.6.1436.
87. Lecumberri E, Goya L, Mateos R, Alía M, Ramos S, Izquierdo-Pulido M, Bravo L. A diet rich in dietary fiber from cocoa improves lipid profile and reduces malondialdehyde in hypercholesterolemic rats. Nutrition. 2007 Apr 1;23(4):332-41. DOI: https://doi.org/10.1016/j.nut.2007.01.013.
88. Fernández-Mar MI, Mateos R, García-Parrilla MC, Puertas B, Cantos-Villar E. Bioactive compounds in wine: Resveratrol, hydroxytyrosol and melatonin: A review. Food Chemistry. 2012 Feb 15;130(4):797-813. DOI: https://doi.org/10.1016/j.foodchem.2011.08.023.
89. de Melo CL, Queiroz MG, Fonseca SG, Bizerra AM, Lemos TL, Melo TS, Santos FA, Rao VS. Oleanolic acid, a natural triterpenoid improves blood glucose tolerance in normal mice and ameliorates visceral obesity in mice fed a high-fat diet. Chem Biol Interact. 2010 Apr 15;185(1):59-65. DOI: https://doi.org/10.1016/j.cbi.2010.02.028.
90. Prior RL, E. Wilkes S, R. Rogers T, Khanal RC, Wu X, Howard LR. Purified blueberry anthocyanins and blueberry juice alter development of obesity in mice fed an obesogenic high-fat diet. J Agric Food Chem. 2010 Feb 11;58(7):3970-6. DOI: 10.1021/jf902852d.
91. Graf D, Seifert S, Jaudszus A, Bub A, Watzl B. Anthocyanin-rich juice lowers serum cholesterol, leptin, and resistin and improves plasma fatty acid composition in fischer rats. Plos One. 2013 Jun 18;8(6):e66690. DOI: https://doi.org/10.1371/journal.pone.0066690.