Chapter

Flavonoids: A Promising Therapy for Obesity Due to the High-Fat Diet

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Abstract

Currently, metabolic diseases are the main public health problem. Obesity is a metabolic imbalance that leads to insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and proinflammatory and prothrombotic states that can trigger type 2 diabetes as well as cardiovascular diseases. Obesity is the excess of adipose tissue and is considered a risk factor to develop metabolic syndrome. The obesogenic environment that is lived promotes the search for specific solutions that help to control, eradicate, or minimize the negative results in health, making use of the properties of flavonoids, as important sources of antioxidants, with anti-inflammatory, antithrombotic, and antihypertensive effects. Given the above, the objective of this chapter is to highlight the effects of flavonoids on the modulation of lipolysis and lipogenesis altered by a hyperlipidic diet.

Keywords: flavonoids, lipolysis, lipogenesis, obesity, inflammation

1. Introduction

Obesity is a major health problem worldwide. It is the result of the combination of genetic factors, inadequate nutrition, and lack of regular physical activity. The ingestion of a diet of high energy density is the main cause of visceral or central obesity, since the excess energy is stored in adipocytes, which increase in size and number, or both, especially the visceral ones, producing an increase in the rate of lipolysis, which, in turn, stimulates the secretion of cytokines by the infiltration of leukocytes, macrophages generating inflammation in the adipocytes, and leads to proinflammatory state, insulin resistance, and endothelial dysfunction. Thus, adipose tissue dysfunction represents the etiopathogenic mechanism (**Figure 1**) in the development of cardiovascular disease, type 2 diabetes, and renal disease initiated by visceral obesity [1].

The WHO defines overweight and obesity as "abnormal or excessive accumulation of fat that can affect health." A person is defined as normal weight if their BMI is 18.5–24.9 kg/m^2, overweight if the BMI is 25–29.9, or obese if the BMI is 30 or more [2].

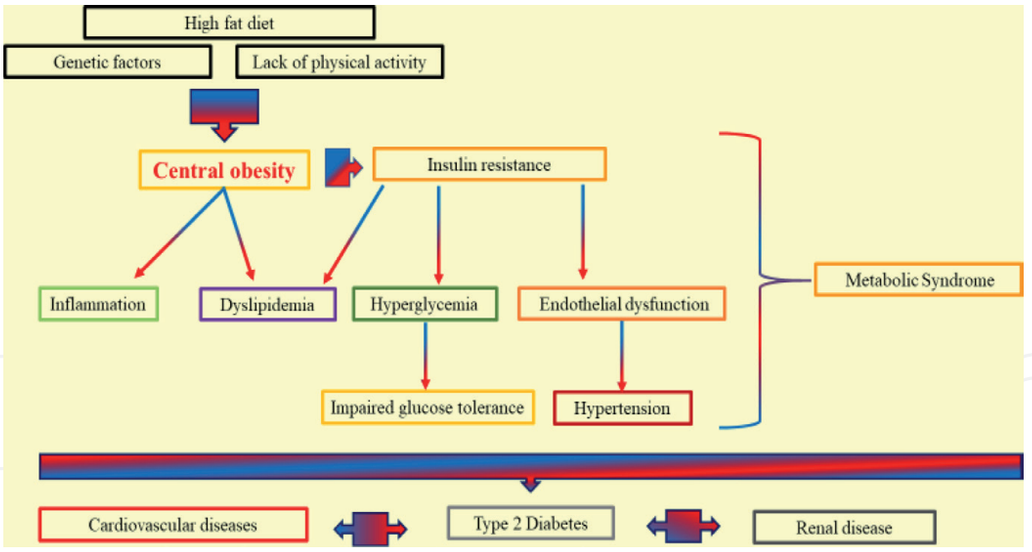

Figure 1.
Etiopathogenic and pathophysiological mechanisms of obesity.

2. Mechanisms present in obesity

The number of adipocytes increases in the early age but reaches a maximum in youth and remains constant regardless of weight changes. In overweight or moderate obesity, the cells grow by the accumulation of lipids, without increasing their number. However, when obesity increases to more severe levels, the number of adipocytes will always increase [3].

Adipose tissue can be made up of large adipocytes (hypertrophy) or many small ones (hyperplasia). These two mechanisms contribute to the expansion of adipose tissue. In adults, hypertrophy is the mechanism that predominates and has been detected, which is strongly related to diet, while hyperplasia depends on genetics [4].

When there is an imbalance between the amount of energy consumed and that used by the body, it begins to store the excess energy in the form of triglycerides inside the adipocytes. These adipocytes begin to become hypertrophic, which causes free fatty acids to be released into the circulation (lipotoxicity), as well as the adipocytes changing their immunological balance which promotes the production of proinflammatory cytokines [5].

Obesity is a chronic state of low-grade inflammation. During the development of obesity, macrophages infiltrate the visceral white adipose tissue, causing chronic inflammation of low intensity that is characterized by the upregulation of proinflammatory adipokines such as TNFα, and decrease the concentration of anti-inflammatory adipokines such as adiponectin. In addition, saturated fatty acids and TNFα, derived from adipocytes and macrophages, result in a cycle that leads to chronic inflammation of fat cells [6], as shown in **Figure 2**.

Also, during obesity, adipose tissue produces a greater amount of reactive oxygen species (ROS) which causes oxidative stress. This stress in turn leads to the abnormal production of adipokines (chronic low-grade inflammation), where it has been shown, for example, that the concentration of adiponectin is inversely related to the concentration of ROS [7].

2.1 Abdominal obesity

The white adipose tissue is metabolically active itself that participates in the metabolic regulation and physiological processes such as the inflammatory response, vascular function, and the secretion of hormones and adipocytokines [8].

Different epidemiological studies have shown that the increase in the consumption of diets high in saturated fats and simple carbohydrates leads to the progressive accumulation of intra-abdominal fat mass, accompanied by alterations in their pattern of adipocytokine secretion and in the homeostasis of the metabolism of lipids [9, 10].

There are two main types of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT) (**Figure 3**). White adipocytes are the most common fat cells, are present in visceral and subcutaneous adipose tissues, and are responsible for the expansion of fat mass in obesity. On the other hand, brown adipocytes are smaller cells that play a central role in the process of thermogenesis; their deposits are mainly focused on the interscapular and perirenal and around the great vessels, although their deposits are limited according to age advances [10].

In the particular case of obesity and the capacity shown by white adipocytes to adapt their metabolism to the energy demands of the organism, it will depend on the BAT to adequately perform its function as an energy reservoir (uptake of circulating fatty acids, esterification, and deposition as triglycerides (TG)) and prevent ectopic deposits of lipids and, therefore, lipotoxicity in tissues such as the liver and

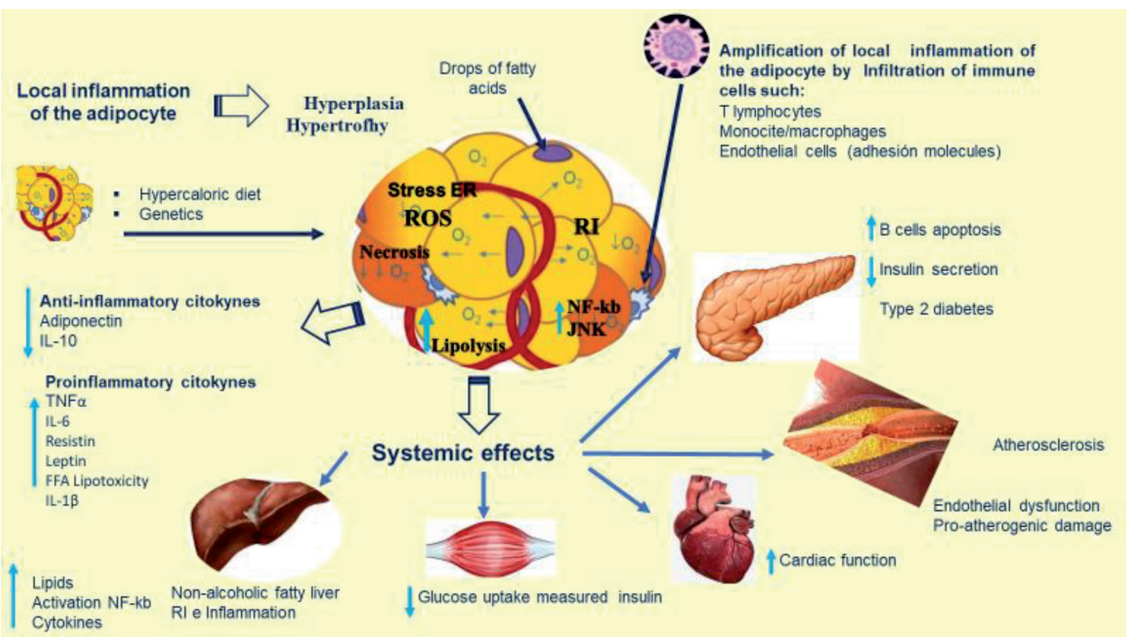

Figure 2.
Mechanisms of inflammation in adipose tissue. ↓Decrease, ↑increase. Interleukin 10 (IL-10), interleukin 6 (IL-6), tumor necrosis factor alpha (TNFα), Jun kinase (JNK), necrosis factor kappa B (NF-κb), free fatty acids (FFA).

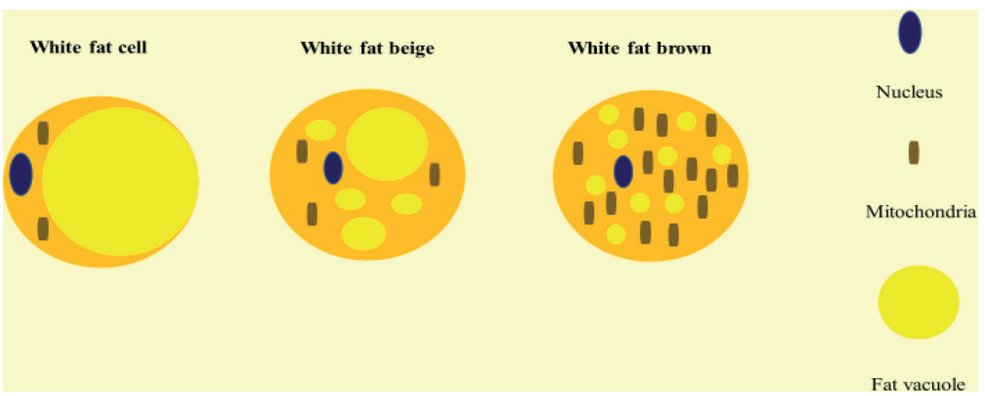

Figure 3.
Types of adipose tissue.

skeletal muscle. It is important to note that in lipogenesis and TG synthesis in the liver due to a hypercaloric diet, the synthesized fatty acids are incorporated into the triacylglycerides, leading to an increase in the synthesis and secretion of very-low-density lipoproteins (VLDL), as shown in **Figure 4**.

When the capacity of the WAT to store TG is exceeded, the activity of lipoprotein lipase of the adipocyte (LPLa) begins to decrease and with it the hydrolysis of TG that is transported by chylomicrons from the small intestine. In the long term, this generates an elevation in plasma levels of triglycerides and c-VLDL. Similarly, the progressive hypertrophy of adipocytes promotes tissue hypoxia, inflammation, and infiltration of macrophages that induce an increase in the secretion of various proinflammatory mediators such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL −6), plasminogen inhibitor 1 (PAI-1), C-reactive protein (CRP), and monocyte chemoattractant protein 1 (MCP-1), among others [11, 12].

The peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor that plays a central role in the regulation of adipogenesis (differentiation and proliferation of adipocytes), allowing the expansion of the TAB in response to a positive energy balance through the increase in the number of small adipocytes with high sensitivity to insulin. In addition to this, PPARγ induces the expression of genes involved in uptake (lipoprotein adipocyte lipase (LPLa)), transport (CD6 fatty acid transporter (FAT/CD36), fatty acid-binding protein in adipocytes (aFABP)), esterification, and deposition of TG (acyl-CoA synthetase (ACS), perilipin 1 (Plin1)) and inhibits the expression of proteins involved in lipolysis (hormone-sensitive lipase (HSL), monoglyceride lipase (MGL)) [13, 14]. The above functions prevent the secretion of free fatty acids (FFA) into portal and systemic circulation and, consequently, lipotoxicity and insulin resistance in peripheral tissues. On the other hand, PPARγ contributes to maintain an adequate sensitivity to insulin through induction in the secretion of adiponectin (ApN) and leptin and the increase in the expression of the substrate of the insulin receptor (IRS1/2) and the transporter GLUT4 [15].

The oxidative function of WAT is generally underestimated. However, this is relevant during the process of differentiation of adipocytes in which the gene expression of PGC-1α is increased, a master regulator of mitochondrial biogenesis and oxidative metabolism [16].

The lipid droplets that are concentrated in the cytoplasm of adipocytes are surrounded by structural proteins and enzymes that respond to hormonal stimuli for lipolysis. Cyclic AMP (cAMP) is a second messenger that activates lipolysis by stimulating protein kinase A (PKA) which, in turn, is responsible for phosphorylating membrane protein perilipin 1 (Plin1). The latter activates the hydrolysis of the

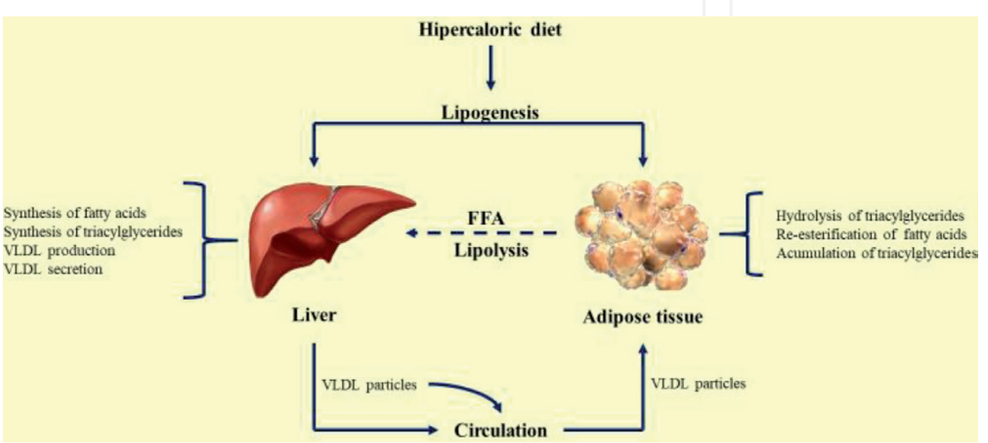

Figure 4.
Lipogenesis stimulation by hypercaloric diets.

TG stored in the lipid vacuoles through the induction of CGI-58, the coactivator of acyl triglyceride lipase (ATGL). Subsequently, PKA activates the hormone-sensitive lipase (HSL) that is responsible for hydrolyzing diacylglycerol (DAG) to monoacylglycerol, which will finally be hydrolyzed to obtain a non-esterified fatty acid (NEFA) and a glycerol molecule [10] (**Figure 5**) [55].

Insulin acts as a physiological inhibitor of catecholamine-induced lipolysis, since after stimulation of the insulin receptor (IRS-1/2) and phosphatidylinositol-3 kinase (PI3K), PKB is activated that phosphorylates phosphodiesterase-3B (PDE-3B) producing the hydrolysis of cAMP. The reduction of cAMP levels and PKB activity that accompany the activation of PDE-3B results in net dephosphorylation and decreased activity of HSL, leading to decreased hydrolysis of stored TAGs [56].

The adequate regulation of the process of lipolysis will lead to the fatty acids released into the circulation being captured by peripheral tissues, activated (addition of an acyl-CoA group), and transported, by carnitine palmitoyl transferase-1 (CPT-1/2), inside the mitochondrial matrix for its oxidation. However, the imbalance that is generated in the metabolism of adipocytes in obesity causes a lipogenic state and insulin resistance that decreases the rate of oxidation and favors lipolysis. The latter favors the ectopic deposits of lipids in the liver, a chronic state of inflammation and systemic resistance to insulin [10].

Abdominal obesity and IR in the WAT promote lipolysis and secretion of FFA into the portal circulation. In addition to this, an increase in plasma concentrations of remnant chylomicrons (rich in TG) is observed due to the absence of LPL induction in the liver and WAT. The hypertriglyceridemia is further accentuated by an increase in the synthesis and secretion of hepatic VLDLs, secondary to an increase in the portal flow of FFA and an increase in the production of apolipoprotein B-100 [17]. The hypertriglyceridemia of MS is directly related to a reduction in the plasma concentration of HDL and an increase in small and dense LDL particles (sdLDL) [18].

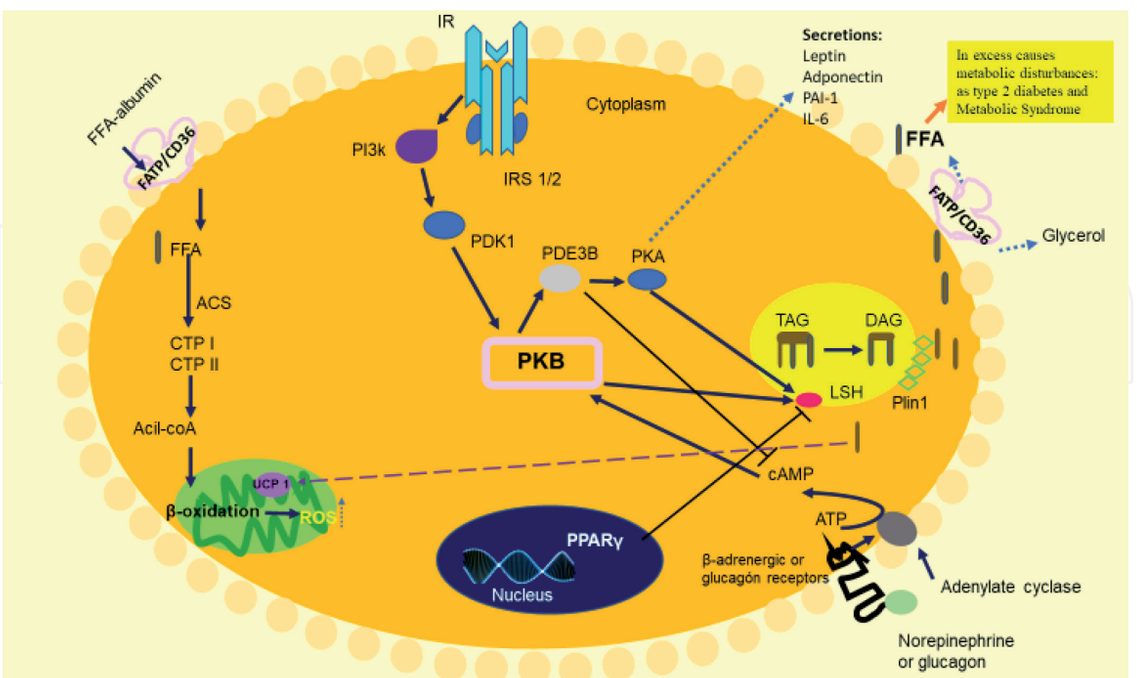

Figure 5.
Control of lipolysis in the human adipocyte. Receptors β y α_{2A}-adrenergic (RA), Kinase A protein (PKA), hormone-sensitive lipase (LSH), insulin receptor (IRS-1/2), Kinase B protein (PKB), kinase (PI3 [PI3-k]), phosphodiesterase type 3B (PDE 3B), kinase protein (PDK1), perilipin (Plin 1), diglyceride (DG), monoglyceride (MG), fatty acid transporter protein (FATP), free fatty acids (FFA), acyl co-A synthetase (ACS), Carnitine palmitoyltransferase (CTP), reactive oxygen species (ROS). The solid arrows indicate the effects that appear beyond the activation of kinases. The sign indicates → stimulation and —| indicates inhibition.

The decrease in plasma levels of HDL is the result of a decrease in the concentration of HDL3 particles (in maturation) and in a greater degree of HDL2 (mature). In hypertriglyceridemia, VLDL becomes prone to the reciprocal transfer of cholesterol esters and triglycerides with HDL2, by the action of cholesterol ester transferase protein (CPTE). This causes the conversion of HDL2 into smaller HDL3 particles rich in triglycerides that become suitable substrates for hepatic lipase (LH).

In IR, the greater induction of LH activity increases the hydrolysis of TG and phospholipids of HDL3 and promotes the formation of even smaller and poor HDL particles in cholesterol esters. They are more susceptible to renal dissociation and excretion of their apolipoprotein A-1 (apoA-1) [19, 20].

The decrease in plasma concentration of HDL reduces the reverse cholesterol transport (RCT) from the peripheral tissues to the liver for biliary excretion. As a result, the atherogenic processes and the elevation in total cholesterol concentrations are favored [19].

At the level of the pancreatic β cell, the accumulation of intracellular cholesterol (due to alterations in the ABCA1 cholesterol transporter) has been shown to influence the reduction of insulin secretion and cellular degeneration that culminates in apoptosis [21].

IR and decreased levels of HDL are related to an increase in sdLDL levels, which have a great atherogenic potential that increases the risk of developing CVD. Its formation is the product of an increase in CPTE activity that favors the exchange of cholesterol esters of LDL by TG of VLDL and consequently the formation of TG-rich LDL particles.

Skeletal muscle is another tissue that undergoes serious metabolic alterations due to the elevation of plasma FFA and TG levels, since it favors the uptake and excessive accumulation of TGIM that diminish mitochondrial oxidation capacity and contribute to the development of IR in this tissue [19, 20].

It has been suggested that the increase in intramyocellular accumulation of lipids is mediated by an increase in the translocation of the FAT/CD36 protein responsible for transporting long-chain fatty acids from the extracellular space to the outer mitochondrial membrane, where it favors its transport by the CPT-1 for its subsequent oxidation. However, when the uptake of fatty acids increases, there is a decrease in the rate of oxidation (by increased levels of malonyl-CoA that inhibit CPT-1) that promotes their accumulation in the form of TG drops. This is directly related to the development of IR and hyperglycemic states, since the accumulation of fatty acid metabolites (long-chain acyl-CoA, DAG, ceramides) induces kinase involved in the phosphorylation of amino acid residues of the insulin receptor or of its substrates resulting in the interruption of the insulin signaling cascade [20, 22].

2.2 Cytokines secreted by fatty tissue

Some of the cytokines secreted by fatty tissue are listed below:

Adiponectin: It is a protein that is synthesized mainly in adipocytes [23] and is the cytokine most secreted by adipose tissue. Its concentration is linked to the ADIPOQ gene [24] and is associated with inflammation processes.

Alpha tumor necrosis factor (TNFα): It is a cytokine that is associated primarily with the inflammatory response related to obesity. It also has an effect on lipid and glucose metabolism [25]. Studies have been conducted in humans with obesity showing high expression of TNFα in adipose tissue and a decreased expression of this factor after losing weight. It has also been shown that TNFα suppresses the transcription of adiponectin [26].

IL-6: It is a cytokine whose synthesis is induced by inflammatory stress and is involved in atherogenesis. It is believed that high levels of IL-6 are responsible for

the increase of proteins in obese patients, particularly CRP. This protein decreases the activity of lipases, which increases lipid consumption by macrophages. It has also been directly associated with IL-6 with the index of body mass, waist circumference, and visceral fat in obese patients [27].

MCP-1: It is a chemokine that is secreted in response to the proinflammatory cytokines that has the function of recruiting monocytes and macrophages in case of inflammation or tissue damage [28]. It is involved with obesity and is secreted by adipose tissue. Normally the adipose tissue of slender people contains 5–10% of macrophages, while in obese the content of macrophages in the adipose tissue can reach as high as 50% of the total cells [6].

PAI-1: It is an inhibitor of serum proteases whose main function is antifibrinolytic (the ability to promote the formation of clots). It has been discovered that this molecule is associated with the differentiation of pre-adipocytes to adipocytes, with the fat content in the vesicles of adipocytes and the level of leptin circulating in plasma [29].

Leptin: It is a hormone produced mainly by adipose tissue that is released into the bloodstream. Leptin levels decrease during fasting; after food intake, leptin is produced which sends a signal to the hypothalamus that inhibits the appetite [30]. However, it has been observed that in obese patients there is a phenomenon of resistance to leptin since in their blood high levels of this hormone have been found.

2.2.1 PPARɣ

Peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to a superfamily of nuclear receptors that regulate the metabolism of glucose and lipids.

PPARɣ is a receptor that is abundantly expressed in adipose tissue and one of the main regulators of glucose and insulin metabolisms. It also plays an important role in the transcriptional activation of adipokines, including adiponectin [31]. PPARɣ directly controls the expression of many genes related to the key functions of adipocytes, such as lipid transport and metabolism, as well as the production of adipokines. It also affects the expression of genes involved with lipid metabolism such as lipid transport (FABP4), fatty acid absorption (LPL, FATP/SLC2/A1, OLR1), recycling of intracellular fatty acids (PEP-CK/PCK1, GK, AQP7), and lipolysis (GPR81) [32].

2.2.2 Oxidized low-density lipoproteins (LDLox)

The increase in vascular production of EROS not only causes a decrease in the synthesis and bioavailability of endothelial NO but also can react and oxidize small, dense low-density lipoproteins (sdLDL) that infiltrate and easily adhere to proteoglycans in the basal vascular lamina [33].

The presence of LDLox constitutes a crucial factor in the development of proinflammatory processes in the arterial vascular wall. Once these molecules are captured by membrane receptors of endothelial cells, they promote a series of proapoptotic and remodeling processes that favor the development of atherosclerosis and endothelial dysfunction. The increase in LDLox concentrations has also been associated with an increase in the proteasomal degradation of eNOS, changes in the ratio of eNOS: iNOS expression and with protein oxidation [34].

Similarly, LDLox are recognized and phagocytosed by macrophages that during the process undergo changes in their conformation and become foam cells. These cells adhere to the smooth muscle cells of the endothelium and continue to accumulate lipids, which favors the formation of lipid striae that progress to form atheromas [35].

It was shown that the incubation of cell cultures with (−)-epicatechin had a protective effect against the oxidative damage generated by the presence of LDLox. This reduces the activation of endothelial cells that promote inflammatory responses (release of cytokines, chemokines, and angiogenic factors) and the production of cell adhesion molecules that facilitate the migration of macrophages to the vascular intima to phagocytose LDLox [36].

2.2.3 Effects of flavanols on hyperglycemia and insulin resistance

In addition to the anti-inflammatory effects that cocoa flavanols have shown, there are recent publications indicating that these also have beneficial effects on hyperglycemia and insulin resistance. These alterations are closely related to dyslipidemia and the presence of abdominal obesity and, consequently, to the pathogenesis of the metabolic syndrome [37, 38].

In a study with hypertensive patients, a vasodilator effect was observed, as well as a decrease in blood pressure and an improvement in blood glucose and fasting and postprandial insulin response, after the daily consumption of dark chocolate rich in flavanols [40, 41].

In another study in mice with type 2 diabetes (DT2) and obesity, it was observed that the administration of cocoa liquor rich in procyanidins (CLPr) decreased the hyperglycemia in a dose-dependent manner. The proposed mechanisms involve an increase in the translocation of GLUT-4 toward the cell membrane, an increase in phosphorylation of AMPK, and the induction of gene expression of UCP-2 in skeletal muscle [39, 40]. Another phenolic compound, ellagic acid, increases the expression of the type 4 glucose transporter (GLUT4) and the peroxisome proliferator-activated gamma receptor (PPAR-γ). Activation of the latter by pioglitazone upregulates adiponectin, but when combined with pure ellagic acid, this positive regulation is achieved at lower drug concentrations, i.e., ellagic acid is responsible for antidiabetic activity [41].

These results are consistent with those obtained in two studies in which it shows that the administration of a flavanol-rich cocoa extract in an animal model with DT2 has hypoglycemic and lipid-lowering effects [39, 42]. In a similar study, it was evaluated whether supplementation of a high-fat diet with CLPr could attenuate the development of obesity, insulin resistance, and hyperglycemia induced by a high-fat diet and that glucose levels were obtained at different doses of CLPr. Plasma fasting decreases, compared to the group fed with a high-fat diet without supplementation. Also, when performing the oral glucose tolerance test, it was observed that supplementation with 2% of CLPr manages to reduce hyperglycemia and postprandial hyperinsulinemia [43].

Phosphatidylinositol-3-kinase (PI3K) and AMPK are the two main molecules involved in the regulation of GLUT4 translocation. Thus, the increase in the activation of AMPK by the administration of CLPr was related to an increase in the expression and translocation of GLUT4 and, therefore, with a higher glucose uptake.

Finally, the effect of the administration of CLPr on the protein expression of UCP1 (brown adipose tissue) and UCP2 (white adipose tissue and liver), involved in the regulation of thermogenesis and energy metabolism, was studied. The results showed that both concentrations of CLPr increase energy expenditure, through an increase in protein expression of UCP1 and UCP2 [44].

2.2.4 Effects of flavanols on alterations in lipid metabolism

Atherogenic dyslipidemia (increased levels of TG, c-LDL, and c-VLDL, accompanied by decreased HDL) not only constitutes one of the central criteria of the

metabolic syndrome but has also been shown to be directly related to the development of CVD. In addition to its beneficial effects on oxidation, inflammation, and endothelial function, cocoa flavanols have also been shown to have lipid-lowering effects that attenuate the development of NCDs associated with alterations in lipid metabolism. There are meta-analyses of clinical trials that have shown that the consumption of products derived from cocoa (cocoa and dark chocolate) has beneficial effects on the lipid profile of patients with some type of CVD or with metabolic risk factors. Most studies are consistent in showing a decrease in plasma levels of CT and c-LDL; however, in relation to the increase in HDL-c levels, the results are heterogeneous [45–47].

Other studies in animals and humans (healthy or with CV risk) have also reported a significant decrease in plasma levels of TG, CT, and c-LDL and an increase in c-HDL levels, after a period of chocolate consumption dark or cocoa [48, 49].

In an animal study, the hypocholesterolemic effects of a mixture of epicatechin and catechin and another mixture of oligomeric procyanidins of cocoa were evaluated, after the ingestion of a high cholesterol diet for 4 weeks. The results showed that only the procyanidin mixture significantly reduced the plasma concentrations of TG and increased the fecal excretion of bile salts and cholesterol, compared to the control group. Through an in vitro study with procyanidin B2, B5, C1, and A2, it was determined that a possible mechanism to explain the previous results is a decrease in the solubility of cholesterol in the micelles that allow intestinal absorption [50, 51].

In a recent in vitro study by Gu et al., the inhibitory effects of cocoa extracts and monomeric, oligomeric, and polymeric flavanols on the activity of pancreatic lipase and phospholipase A2 were evaluated. The results showed that the different extracts had inhibitory effects on the activity of both enzymes and that said effects are proportional to the total polyphenol content and the degree of polymerization of the flavanols [52].

In the liver, alterations in lipid metabolism promote an increase in its fatty infiltration and lipotoxicity that culminate in the development of nonalcoholic steatohepatitis (NASH), one of the most severe comorbidities of the metabolic syndrome [40, 54]. In an experimental study with rats, the preventive or palliative effects that cocoa supplementation could have on the development of NASH induced by a diet high in fat and deficient in choline were evaluated. The results showed that the supplementation with cocoa reduces the degree of steatosis, liver fibrosis, and portal inflammation. In this same study, it was observed that the supplementation with cocoa reduced the accumulation of fat in the liver, due to an increase in the levels of gene and protein expression of the fatty acid-binding protein (LFABP) in the hepatocytes of rats with NASH.

Another flavonoid that has positive effects in obesity is morin, suppressing lipogenesis, gluconeogenesis, inflammation, and oxidative stress, tending to modify the concentration of triacylglycerides in the liver.

A preclinical study showed that morin acts as an inhibitor of fatty acid synthase (FAS) by regulating the SREBP1-c protein binding element, in addition to regulating the liver increase of carnitine palmitoyl transferase 1a (CPT1a) [51, 52].

It is important to mention that morin could interact with various receptors involved in metabolic diseases as well as ligand of altered genes in obesity and therefore in the present inflammation. However, the mechanism of action of the flavonoid is still unknown since there are no major reports of research related to the mechanism and effect of it.

2.2.4.1 Effect of flavonoids of marine algae on obesity

The content of flavonoids in *Undaria pinnatifida* is equivalent to 42% of the total phenols, and several studies have shown that the main phenolic compounds

and flavonoids contained in this alga are rutin, caffeic acid, catechol, quercetin, and morin with approximately 3.1 mg/g of sample. Although there are not many reports regarding the content of flavonoids in Undaria, in other brown algae, the content varies from 0.9 to 6.3 mg/g of sample [53].

2.2.4.2 Effects of flavonoids on body fat

The content of epididymal adipose tissue (ATe), retroperitoneal (ATr), mesenteric (ATm), and total (%) is modified by the intake of phenols from marine algae, such that in the standard group with 5.10% adipose tissue, and the group that was given a high-fat diet, 11.33% was reached, in contrast to the group that consumed free phenols, the content was reduced to 8.9%.

The effect of the phenols was the reduction of the concentrations of triacylglycerols in 57% with respect to the group fed with a high-fat diet; only 10% above the group was fed a normal diet. In relation to changes in total cholesterol levels, phenols decreased it by 75% with respect to the group with a high-fat diet, remaining only above the group with a normal diet by 20% [58].

2.2.4.3 Clinical studies on the effect of flavonoids

Recent studies have shown the importance of the intake of flavonoids and their relation to the risk of chronic diseases, where the intake of flavonoids and obesity were inversely associated in both men and women using multivariate models in a study in the USA. Adults in the highest quartile of flavonoid intake had a significantly lower body mass index and waist circumference than those in the lowest quartile of flavonoid intake ($P < 0.03$ and $P < 0.04$, respectively); and the ingestion of flavonoids was inversely related to the levels of C-reactive protein in women (trend p, 0.01). These findings support a growing evidence that the consumption of flavonoids may be beneficial for the prevention of diseases [57].

Scientific evidence has been found in clinical studies of the effect of flavonoids present in fruits that can be consumed regularly and be part of the diet, suggesting a beneficial effect for health, as is the case of anthocyanins, punicalagin, and ellagic acid, present in the pomegranate fruit.

The effect of flavonoids present in pomegranate juice on the function of adipocytes has been studied. Using increasing doses of juice and by radiometric methods, the activity of the amino oxidase was determined, and with colorimetric methods the influence of the juice on the lipogenic and lipolytic activities of the human adipose tissue was evaluated. The results showed a dose-dependent response of juice to inhibit the monoamine oxidase and the activity of the amino oxidases present in the human adipose tissue sensitive to semicarbazide. The juice also inhibits lipogenesis and lipolysis in human and mouse adipose cells [58].

Oral supplementation with pomegranate extract on biomarkers of inflammation and oxidative stress in plasma, as well as serum metabolic profiles in overweight and obese people, for 30 days, resulted in a significant decrease in serum glucose, insulin, and blood levels, total cholesterol, concentration of low density lipoproteins LDL-c, MDA and IL-6. It is concluded that the consumption of pomegranate extract can reduce complications related to obesity [59].

The functionality of flavonoids in various diseases has been demonstrated, and these have been part of our diet all the time, since they are found abundantly in fruits, vegetables, and grains that we consume, such as apples, grapes, blueberries, pomegranates, oranges, broccoli, spinach, thyme, cocoa, nuts, and soybeans, to name a few.

However, the concern that the benefits of these compounds have aroused in the food industry is wide, since, from these natural sources, products containing

flavonoids are manufactured, enriching, fortifying, or increasing the concentration of flavonoids present in various products to have a positive effect on health. In the market there are various products rich in flavonoids such as fruit and vegetable juices, wines, cereals, milk formulas, soy milk, almond milk, confectionery, rice drinks, relaxing drinks, food supplements, and capsules containing extracts of flavonoids. The development of new functional products is increased due to the need to contribute to the health welfare.

3. Conclusions

Although there is sufficient evidence on the beneficial effect of flavonoids in relation to the improvement in health status in metabolic diseases such as obesity, where flavonoids contribute to recover the lost balance due to the deregulation of lipogenesis and lipolysis, much remains to be done to clarify aspects such as the adequate concentrations suitable for use in drug design, the interactions between the different compounds present, as well as the modifications in the absorption of them depending on the changes in the health states. It is also necessary to deepen into the reaction mechanisms involved for a better management of these compounds according to each pathology.

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Conflict of interest

There is no conflict of interest to declare.

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