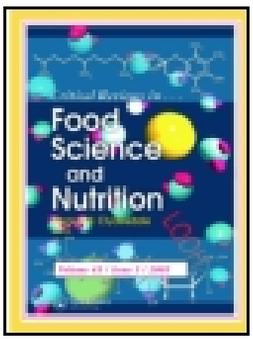

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REVIEW

Association between obesity and breast cancer: Molecular bases and the effect of flavonoids in signaling pathways

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ABSTRACT

Obesity is an abnormal or excessive accumulation of fat that leads to different health problems, such as cancer, where the adipocytes promote the proliferation, migration, and invasion of cancer cells, especially in the breast, where the epithelial cells are immersed in a fatty environment, and the interactions between these two types of cells involve, not only adipokines but also local pro-inflammatory mechanisms and hypoxic processes generating anti-apoptotic signals, which are a common result in leptin signaling. The expression of the Vascular Endothelial Growth Factor (*VEGF*) and cyclin *D1*, results in the decrease in phosphorylation of *AMPK*, increasing the activity of the aromatase enzyme; alternatively, the adiponectin activates *AMPK* to reduce inflammation. Nevertheless, alterations of the *JAK/STAT* pathways contribute to mammary carcinogenesis, while the *PI3K/AKT/mTOR* pathway controls most of the cancer's characteristics such as the cell cycle, survival, differentiation, proliferation, motility, metabolism, and genetic stability. Therefore, the purpose of the present review is, through the accumulated scientific evidence, to find the concordance between the signaling pathways involved among obesity and breast cancer, which can be modulated by using flavonoids.

KEYWORDS

Adipokines; Estrogens; Flavonoids; Obesity; Signaling Pathways

Introduction

In prospective epidemiological studies, the frequency of chromosomal instability in lymphocytes is predictive of cancer risk and, patients with different types of cancer show increased chromosomal instability at the time of diagnosis (Vodicka et al. 2015); however, in recent years, many *RNA*-binding proteins (*RBP*) and non-coding *RNAs* have emerged as key players in the development of tumors (Bisogno et al. 2018). Immunopathologically, breast cancer is usually grouped into a) positive estrogen receptors (*ER+*) such as cell lines *MCF-7 and T47D*, b) negative estrogen receptors (*ER-*) such as cell lines *SKBR3*, *MDA-MB-453*, *MDA-MB-231* y *MDA-MB-68* and c) based on other biomarkers, such as the progesterone receptor (*PR*), receptor 2 of human epidermal growth factor (*HER2*). Additionally, breast cancer is also classified according to the gene expression profiling, the phenotype of the tumors and the susceptibility to therapy, which drives the classification into different molecular subtypes, such as luminal A (*ER+*, *PR+*, *HER2-*), luminal B (*ER+*, *PR+*, *HER2+*) and basal phenotypes (*BLBC*). The expression of the estrogen receptor (*ER*), the progesterone receptor (*PR*), and *HER2* conventionally determine the therapeutic response and prognosis of breast cancer. Tumors with overexpressed *HER2* are the target of trastuzumab (human monoclonal antibody), which blocks *HER2*. In contrast, none of the three breast cancer markers (*ER*, *PR* and *HER2*) are expressed in *BLBC*. These patients are defined as cases of triple negative breast cancer (*TNBC*) or negative phenotype (*ER-*, *PR-*, *HER2-*) and this represents the most aggressive subclass (Erturk et al. 2015; Nassar, Nasr, and Talhouk 2017; Hasanpourghadi, Pandurangan, and Mustafa 2018; Iqbal et al. 2018).

Obesity

The ability to store excess energy as adipose tissue is an adaptation that allows to survive periods of nutritional deprivation; however, obesity which is an abnormal or excessive accumulation of fat leads to various health problems. According to the World Health Organization (WHO), obesity is defined as a body mass index (BMI) equal to or greater than 30 kg/m^2 and it is estimated that >1.3 billion people worldwide are obese (S. Khan et al. 2013; Khandekar, Cohen, and Spiegelman 2011; Hosney et al. 2017) increasing 3 times or more since 1980 (Font-Burgada, Sun, and Karin 2016). The prevalence of obesity has increased at an

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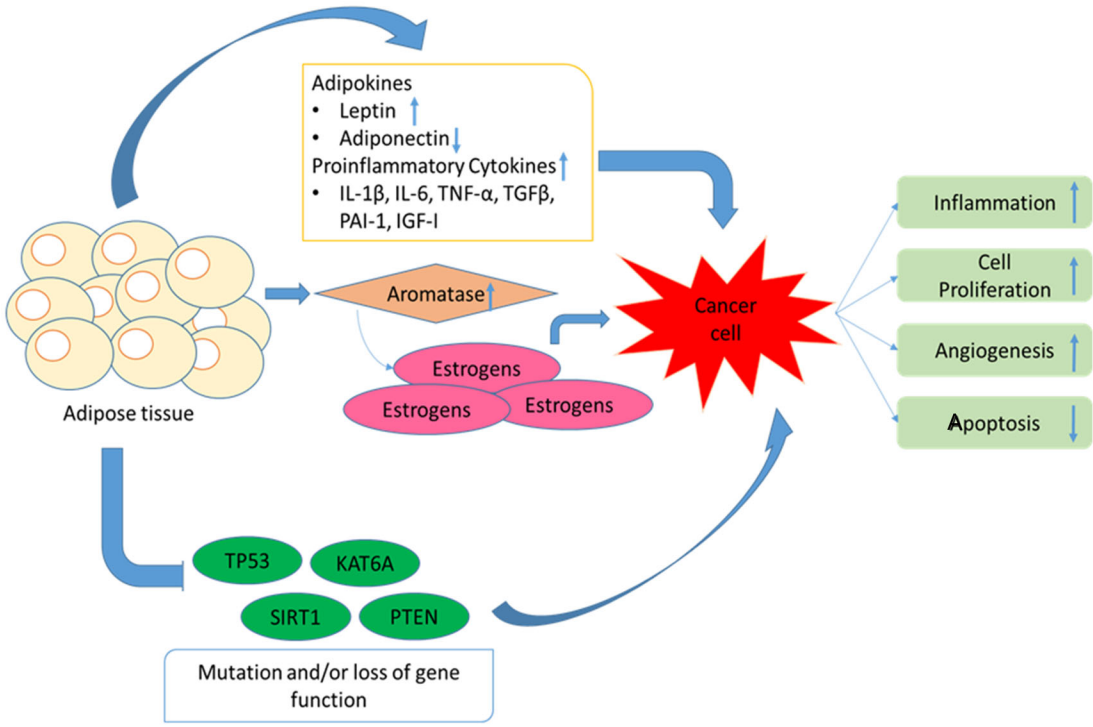

Figure 1. Adipose tissue present in postmenopausal obese women secretes adipokines and proinflammatory cytokines, increasing the expression of proteins involved in angiogenic and antiapoptotic processes causing the loss of the function of tumor suppressor genes, leading to inflammation and cell proliferation. The adipocytes present in the tumor microenvironment can also promote the activity of aromatase and estrogens which, being over-expressed, promote the differentiation of normal cells into cancer cells.

alarming rate worldwide, reaching pandemic proportions in the last two decades. In obesity, excess adipose tissue has been shown to be a risk factor for the development of several types of diseases, such as diabetes mellitus type 2 (DM2), cardiovascular disorders, hypertension, and certain types of cancer, demonstrating that adipocytes promote proliferation, migration, and the invasion of malignant cells (Carter and Church 2012; Hoy, Balaban, and Saunders 2017; Bertolini 2013; Barone et al. 2016; Jardé et al. 2011), among them prostate and stomach cancer in men, breast (postmenopausal), cervical, uterine, endometrial, and ovarian cancer in women, and kidney and colon cancer, adenocarcinoma of the esophagus, pancreas, gallbladder, thyroid, and liver cancer in both sexes (Lengyel et al. 2018; Yoon et al. 2019; Spyrou et al. 2018; Colditz and Lindsay 2018). Risk factors for the development of breast cancer include, among others, hormonal, reproductive and obesity factors. Understanding the mechanism by which obesity can lead to the onset and progression of cancer is essential for the development of effective therapies for obese patients with cancer (Lalloo and Evans 2012; Kolb, Sutterwala, and Zhang 2016).

Adipose tissue is classified as white adipose tissue (WAT), beige adipose tissue, brown adipose tissue (BAT), and pink adipose tissue (PAT) that show different regulatory, morphological and functional characteristics of their adipocytes and immune cells. The adipocytes of WAT and BAT play a key role, not only in the control of energy homeostasis through the balance between storage and energy expenditure, but also by modulating immune and inflammatory responses (Corrêa, Heyn, and Magalhaes 2019).

The increase in the incidence of cancer due to obesity, as well as the deaths that maintain the obesity-cancer relationship have been established in recent decades, estimating that 14% of cancer deaths in men and 20% in women are attributable to obesity (Kolb, Sutterwala, and Zhang 2016; Hosney et al. 2017)

Association between obesity and breast cancer

WAT adipocytes and other stromal cells serve as a source of bioactive molecules that regulate important signaling pathways that contribute to the initiation and promotion of cancer (Lengyel et al. 2018; Bonan and DeCicco-Skinner 2018). The main pathways that connect obesity with malignant tumors include a) insulin resistance (IR) and hyperinsulinemia, b) abnormalities in the insulin-like growth factor 1 system (*IGF-1*), c) oxidative stress and chronic low-grade systemic inflammation, d) impaired immune function, e) impact of obesity on the biosynthesis of sex hormones, f) abnormal variations in adipokine levels (Figure 1) (Spyrou et al. 2018) in addition to growth factors, alterations in the pathophysiology of the adipocyte, deposition of ectopic fat, alterations in the microenvironment as well as cellular disturbances and alterations in the circardian rythm and diet, in addition to the kynurenine pathway (Lengyel et al. 2018)

The breast is a specific organ in which the epithelial cells are immersed in a fatty environment. Therefore, the epithelial tissue, whether healthy or tumoral, is directly in contact with the fat cells, and the interactions between these cell types can stimulate angiogenesis and cell proliferation that

involves, not only adipokines, but also local pro-inflammatory mechanisms and hypoxic processes (Delort et al. 2015).

Adipose tissue is relevant in the case of breast cancer, where there is a strong association between the amount of breast adipose tissue that is equivalent to breast size, breast cell density and the risk of this cancer throughout life. (Stone, McPherson and Darlington 2018), it also constitutes a large proportion of the tumor tissue, with cancer-associated adipocytes (CAA) being the predominant cell population in the stromal behavior of breast cancer (Incio et al. 2018). In the CAAs, triglycerides are hydrolyzed to release free fatty acids (FAs) by sequential action of the triglyceride-adipose lipase, the hormone-sensitive lipase, and the monoacylglycerol lipase. Hypoxia, through hypoxia-inducible factor 1α (*HIF-1α*), increases lipid uptake in cancer cells by inducing the expression of *FABP3/4*, as well as adipophilin, a structural protein of lipid droplets (Lengyel et al. 2018). During obesity, there is a significant increase in myofibroblasts, which act by depositing rigid matrix components such as fibronectin and fibrillar collagen, supporting tumor establishment and inducing fibrosis in the WAT (Corrêa, Heyn, and Magalhaes 2019). The increase in tissue stiffness and the mechanotransduction of fibrotic tissue can be an important contributor to tumorigenesis. Adipocytes and adipose-derived stromal cells (ASCs) secrete extracellular matrix (ECM) molecules that include fibronectin, laminin, and collagens. A cleavage product of collagen VI, the ECM molecule of the most abundant WAT, is implicated in both tumorigenesis and breast cancer progression (Lengyel et al., 2018). Among the many types of cells that surround breast cancer cells, the most abundant are those that constitute the adipose breast tissue, mainly mature adipocytes and progenitors (Y. Y. Wang et al. 2012). Both progenitor and mature adipocytes are not passive toward breast cancer cells and they exhibit specific features that are beginning to be characterized, such as their capacity to contribute to local inflammation through the secretion of *IL-6* promoting tumor growth when regulating positively anti-apoptotic and angiogenic proteins in tumor cells (Y. Y. Wang et al. 2012; Nicolini, Carpi, and Rossi 2006).

There is also a complex relationship between the adipose tissue and angiogenesis, by which fat cells synthesize angiogenic growth factors, to a large extent proteins, thus neovascularization is essential for *de novo* adipogenesis (Vona-Davis and Rose 2009). An important result of this metabolic change is the activation of pathways that generate macromolecules by building blocks to support proliferation, including fatty acids and complex lipids for membrane synthesis, nucleotides for *DNA/RNA* synthesis and amino acids for the synthesis of proteins (Balaban et al. 2017).

The kynurenine pathway is the dominant pathway of the tryptophan catabolism and represents the elimination of about 95% of tryptophan not used in the protein synthesis. It is initiated by the oxidative enzymes indoleamine-2,3-dioxygenase (*IDO*) and tryptophan-2,3-dioxygenated (*TDO*), while the latter is a liver enzyme, the *IDO* by interferon-γ, drives the pathway as part of the infection response and immune system stimulation, although it is also physiologically driven when eating (Stone, McPherson and Darlington 2018). A key factor that involves kynurenines in cancer, is that the kynurenine is an important activator of the Aryl hydrocarbon receptor (*AHR*), and when it is active, it is related to several types of cancer, including breast cancer, since it promotes the development of Treg cells, suppresses the activity of effector T cells, and therefore, promotes the development and progression of the tumor. It is known that the kynurenine pathway is regulated on the increase in *TNBC* cells. This seems to include not only *IDO*, but also *TDO2*, whose expression depends on *NF-κB*. The increase in the generation of kynurenine is enough to activate the *AHR*, and to contribute to the progression of cancer and metastasis (Stone, McPherson and Darlington 2018).

Adipose tissue in obesity and cancer

The links between obesity and breast cancer are, among others, hyperinsulinemia, estrogen signaling, inflammation and the expression of adipokines, such as leptin, resistin, and adiponectin (Figure 1) (Hosney et al. 2017; Barone et al. 2016), in addition to other factors derived from adipose tissue that activate key inflammatory molecules such as *NF-κB* and *STAT3*. The activation of *NF-κB* in the adipose tissue induces the expression of several pro-inflammatory mediators (*COX-2*, *TNF-α*, and interleukins (*IL*) -6, -8 and *-1β*) that induce the expression and activity of the aromatase. The activation of these inflammatory mediators leads to the alteration of the expression of genes involved in breast carcinogenesis (Figure 2) (S. Khan et al. 2013; X. Wang, Simpson, and Brown 2015). The adipocytes of invasive tumors have greater expression of anti-inflammatory genes such as *MARCO* and *VISG4* and, such increased immune tolerance provides a tumor microenvironment for tumorigenesis. This is how adipocytes of breast cancer tumors have high levels of versican (intimately related to tumorigenic behavior), *CD44, AdipoR1,* and lower levels of adiponectin and perilipins. Furthermore, macrophages in Crown-like structures (*CLS*) (derived from adipose tissue that promotes adipogenesis and inflammation in the white adipose tissue), phagocytose cellular debris and lipid drops, releasing triglycerides and fatty acids, which produce reactive oxygen and nitrogen species, which can act as mutagens (Choi, Cha, and Koo 2018).

Adipose tissue, being an endocrine tissue, can regulate the production and bioavailability of sex hormones, which can mediate the association of obesity with the risk of breast cancer through, a) aromatase expression that transforms androgens into estrogens, less active (androstenedione, estrone) to more potent hormonal forms (testosterone and estradiol), and b) by the increase in the bioavailability of estradiol and free testosterone through hyperinsulinemia, increasing the bioavailability of *IGF-1,* and decreasing liver secretion of the sex hormone-binding globulin (*SHBG*) (Christodoulatos et al. 2019; Colditz and Lindsay 2018). *IGFs* are directly responsible for stimulating cell growth and proliferation through the signaling of the insulin-like growth factor 1 receptor (*IGF-R1*)/*MAPK*. Binding of *IGF-1* to its receptor can activate *MAPK, mTOR* signaling, inhibit *p53* or

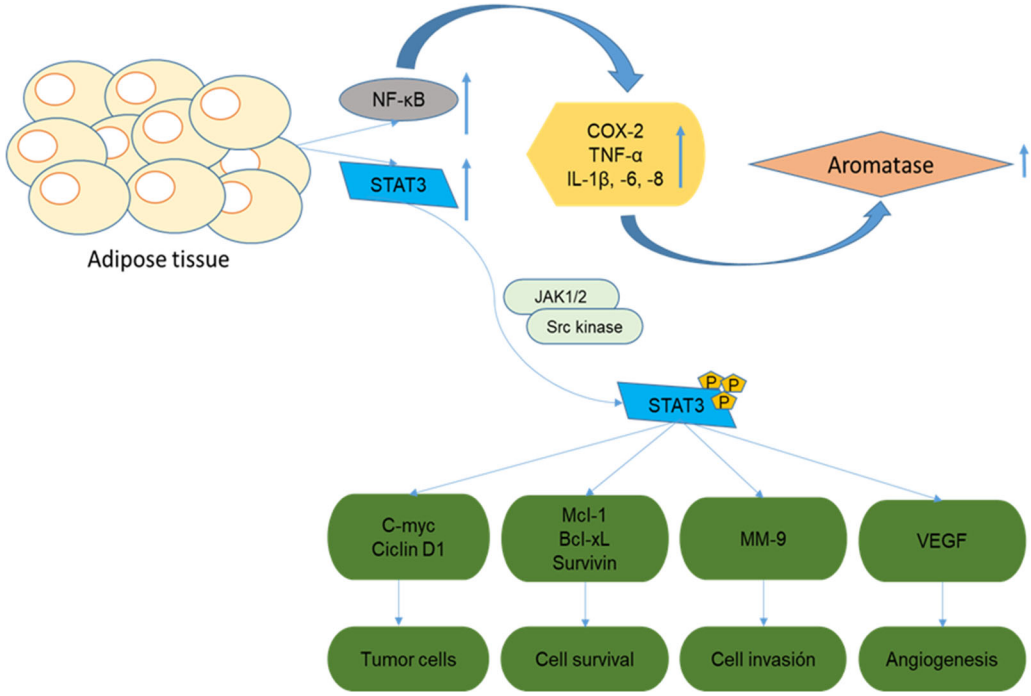

Figure 2. Activation of inflammatory molecules such as *NF-κB* and *STAT3*. The activation of *NF-κB* secreted by adipose tissue, induces the expression of several proinflammatory mediators (*COX-2*, *TNF-α* and interleukin (*IL*) *-6*, *-8*, *-1β*) that cause the activation of aromatase. The adipose tissue also secretes *STAT3*, which undergoes phosphorylation in *Tyr705*, mediated by the activation of non-receptor kinases (*JAK-1*, *JAK-2* and *Src* kinase). The phosphorylation of *STAT3* positive regulates the expression of genes involved in the proliferation, survival, invasion and angiogenesis of cancer cells.

stimulate *HIF-1α* expression. The result of these pathways is cell death evasion, cell growth, cell proliferation, angiogenesis, and metastasis (Bonan and DeCicco-Skinner 2018).

Adipocytes adjacent to cancer cells have smaller lipid droplets unlike adipocytes farthest from the tumor. The increase in the use of lipids, unlike glucose, is a hallmark of cancer aggressiveness (Lengyel et al., 2018). FAs that produce approximately twice the energy of glucose, are the main form of lipids used by tumors as a source of energy through *β*-oxidation. Tumor cells synthesize most of the *de novo* FAs, despite a sufficient supply of lipids provided by the diet. The increased lipogenesis is a hallmark of many types of aggressive cancer. Lipogenesis inhibitors reduce the viability of cancer cells only in the absence of exogenous lipids (Lengyel et al., 2018). The acquisition of resistance to therapy has been linked to the activation of lipid metabolism in cancer cells, and evidence links the absorption of adipocyte-derived FAs in the epithelial–mesenchymal transition (EMT). Lipolytic changes in the adipose microenvironment lead to the release of fatty acids from adipocytes, which have been linked to the invasion of pancreatic, prostate, and breast cancer (Lengyel et al., 2018). The increase of brown adipocytes in the WAT promotes an anti-inflammatory phenotype that characterizes the development of healthy tissue and in turn, decreases the IR, increasing thermogenesis and, therefore, reducing obesity. This can be achieved by a process called browning that occurs when the adipose tissue is exposed to certain stimuli such as cold, microbiota modifications or receptor activation, such as androgens (*ADRB3*), undergoing morphological and functional changes, in which the WAT acquires characteristics of the BAT (Corrêa, Heyn, and Magalhaes 2019). Adipocytes of the beige adipose tissue have a high capacity for dissipation of thermogenic energy uncoupled through the *β*-oxidation of fatty acids (Lengyel et al., 2018).

While obesity is associated with the development of cancer, patients with high-grade cancer are in fact, often lipodystrophic. Even patients in advanced stages of cancer are often affected by a multifactorial syndrome called cachexia (Duval et al. 2018), which is a complex disorder, driven by inflammation and metabolic imbalances (Daas, Rizeq, and Nasrallah 2019) resulting in the continuous loss of skeletal muscle and fat mass that cannot be reversed with conventional nutritional support. Cancer cachexia occurs in approximately 80% of cancer patients and it is the leading cause of death with 22-30% of all cancer patients (Han et al. 2018; Shyh-Chang 2017). Browning of the WAT affects metabolism by increasing heat production, resulting in a decrease in fat, while in contrast, it participates in the process of development of cancer cachexia. Two driving factors, the *IL-6* and the parathyroid hormone-related protein (*PTHrP*), are secreted by the tumor, primarily through the sympathetic nervous system to release norepinephrine, and to act on the adipocyte *β3* adrenergic receptor by activating other factors of transcription leading to gene expression of the uncoupling protein 1 (*UCP1*), which increases during the process of browning WAT (Guang and Wang 2018). Adipocytes release *TNF-α* and other factors that have a direct effect on muscle metabolism. Similarly, skeletal muscle also releases *IL-6, IL-1β*, and other signals that interfere with lipid metabolism. These procatectic mediators play a key role in some signaling pathways, such as *NF-κB, p38, MAPK,* and *STAT3*, which, when altered, are associated with multiple cytokine signals that mediate the pathogenesis of

adipose tissue in cancer cachexia. When a phenotypic change occurs due to the process of browning WAT in cancer-associated cachexia, which occurs in the early stages, prior to the development of skeletal muscle atrophy, it seems to indicate that the WAT dysfunction is an essential contributor to cachexia, although this must be verified (Daas, Rizeq, and Nasrallah 2019).

In addition, for non-tumor patients, the reinforcement of lipolysis and the loss of WAT will stimulate other approaches, such as increasing leptin levels to promote anabolism and energy intake. However, the level of leptin in patients with cancer cachexia is relatively low, but the appetite of patients does not increase as feedback due to this low level, so this feedback mechanism of patients with cancer cachexia is disrupted, which is probably associated with systemic inflammation (Guang and Wang 2018). Moreover, irisin stimulates the process of browning WAT through specific actions in the adipocyte population, as well as inducing the expression of thermogenic genes in mature adipocytes in cancer cachexia (Daas, Rizeq, and Nasrallah 2019).

Adipokines

Adipokines can act in the breast tissue in an endocrine way (external pathway through adipocyte deposits), in paracrine ways (through breast adipose tissue and non-adipose sources, including stromal cells and inflammatory cells) and in autocrine action (through breast tumor, by itself) (Jardé et al., 2011). The structure of the mammary gland favors the close interaction between the breast adipose tissue and the breast tissue, suggesting that adipokines produced by breast adipose tissue and the tumor microenvironment may be the main link between obesity, the progression of the disease, and metastasis (Ray and Cleary 2017). The adipokines secreted by adipocytes increase the gene expression of *NF-κB* and cyclin-D1, inducing anti-apoptotic transcription and stabilizing pro-oncogenic factors such as *β*-catenin and cyclin-dependent kinase (*CDK*) 6, which may contribute to tumorigenesis (Choi, Cha, and Koo 2018).

While the large number of circulating proinflammatory adipokines, such as leptin, *TNF-α,* resistin, and extracellular Nampt (*eNampt*) are high in tumors, some others, such as adiponectin and omentin-1, are low in tumors, so they are considered to be protective against carcinogenesis (Spyrou et al. 2018). Among adipokines, adiponectin and leptin have been the most studied, while *IL-6*, *TNF-α,* and resistin are relatively less studied. Some studies have shown that adiponectin levels are low, and leptin, *IL-6*, *TNF-α,* and resistin levels are high in obesity related to the aforementioned types of cancer (Yoon et al., 2019). In addition to these, more than 10 adipokines present in obesity and linked to the development of breast cancer have been reported (Spyrou et al. 2018; Christodoulatos et al. 2019), including apelin, quemerin, lipocalin 2, oncostatin M, osteopontin, irisin, and retinol binding protein 4 (*RBP4*), whose mechanism of action, as well as their effect are shown in Table 1.

Leptin

This adipokine is a product of the *ob* gene, mainly produced by adipocytes. It is a regulator of food intake, and its effects on inflammation, immunity and cell proliferation have been demonstrated. High levels of leptin are correlated with obesity, and this one with cancer, for example, several cancer-associated fibroblasts (CAFs) and matrix metalloproteinases (MMPs) are involved in different stages of cancer progression, which include invasion and metastasis, thus, it could be a key modulator in the development of breast cancer due to its specific structure, given that leptin has been shown to stimulate cell proliferation of both normal and cancer cells, in addition to its anti-apoptotic effect in the latter (Newman and Gonzalez-Perez 2014; Delort et al. 2015; S. Khan et al. 2013; Pérez-Pérez et al. 2017; Hosney et al. 2017; Ray and Cleary 2017).

Adipokines act through their receptors on breast tumor cells to influence proliferation, migration and invasion in breast cancer; the production of proteins derived from the epithelium, angiogenic proteins and growth factors, stimulating other cells in the tumor microenvironment to invade and proliferate. This is expressed not only in the cancerous tissue, but also in the normal tissue surrounding the tumor. Accordingly, the *mRNA* of the *Ob-R* receptor and protein expression have been characterized in different breast cancer cell lines, including *MCF-7, MDA-MB-231* and *T47D*. The binding of leptin to the extracellular domain of the long leptin receptor (*ObR*) isoform leads to the activation of multiple downstream intracellular signaling pathways, including the *JAK/STAT3* signal transducer, *MAPK*, and the *PI3K/AKT* pathways leading to cell proliferation and survival of breast cancer (Figure 3) (Barone et al. 2016; Jardé et al. 2011; S. Khan et al. 2013; Naylor and Petri 2016; Hosney et al. 2017). Leptin increases the expression of anti-apoptotic proteins, inflammatory markers (*TNF-α* and *IL-6*), angiogenic factors (*VEGF*), and *HIF-1α* (Spyrou et al. 2018). Leptin has effects through its receptor expressed on most tissues, affecting multiple signaling pathways, including *JAK/STAT3, MAPK, PI3K/AKT, ERK1/2, AMPK,* and the insulin receptor substrate (*IRS*). *ERK* signaling pathway promotes the activation of transcription factors that induce cell division. However, after stimulation of *JAK2, PI3K/AKT* are activated, affecting glucose metabolism, cell growth, proliferation, and apoptosis (Christodoulatos et al. 2019; Bonan and DeCicco-Skinner 2018). Leptin also promotes the EMT in *MCF-7, SK-BR-3* and *MDA-MB-468* breast cancer cell lines through the positive regulation of the expression of pyruvate kinase M2 through the activation of the signaling pathway *PI3K/AKT* (Hoy, Balaban, and Saunders 2017). In *ER+* breast cancer cell lines, leptin exerts a direct stimulus on *ERα*, improving aromatase expression and suppressing *p53* (Spyrou et al. 2018; Christodoulatos et al. 2019).

The activation of *JAK2* after leptin binding, leads to the activation of *AKT/PI3K,* and at the same time *PI3K* activates *mTOR* and *p38 MAPK*. The signaling of *mTOR* is involved in the differentiation of *CD4+ T* cells in Tregs cells. Leptin stimulates *mTOR* signaling, which, if it increases above the threshold (as in the case of inflammatory release of leptin), results in the inhibition of Treg cells differentiation. Both

Table 1. Mechanism of action and the effect of adipokines in breast cancer related to obesity.

Adipokine	Expression in cancer	Mechanism	Effect	Reference
Leptin	High	It positively regulates the expression of anti-apoptotic proteins (*Bcl-2*) and inflammatory markers (*TNF-α*, *IL-6*), *HIF-1α*, angiogenic factors (*VEGF*) and stimulates the *JAK/STAT3*, and *PI3K* signaling pathways. Activation of *β*-oxidation of fatty acids through *CPT1B*.	Cell proliferation, angiogenesis, invasion, inflammation, aromatase expression, direct *ERα* activation, *p53* suppression. Induction of chemotherapy resistance.	Beloribi-Djefaflia, Vasseur, and Guillaumond (2016); Christodoulatos et al. (2019); Spyrou et al. (2018)
Adiponectin	Low	Activation of the *AMPK/LKB1* signaling pathway. By binding to the receptor, it facilitates the translocation of the *LKB1/STE20* (*STRAD*)/*MO25*-related adaptor protein from the nucleus to the cytoplasm and promotes phosphorylation of *LKB1*, activating *AMPK* from *MAPK*, *PI3K/AKT*, *WNT-β-* Catenin, *NF-κB*, and *JAK2/STAT3*.	The effect depends on the state of the estrogen receptor. In ER positive cells, there is suppression of cell growth, inhibition of proliferation, migration and invasion. In *ER*-cells, they promote proliferation.	Christodoulatos et al. (2019)
Visfatin/eNampt	High	Activation of *NF-κB*, positive regulation of Notch-1, cyclin *D1*, *CDK2*, *MAPK*, *ERK1/2*, and *p38* signaling pathways.	Promotion of inflammatory processes, induction of cell proliferation, inhibition of apoptosis and angiogenic effects.	Christodoulatos et al. (2019); Spyrou et al. (2018)
Apelin	High	Endogenous ligand that binds to the G-protein coupled receptor that results in the activation of the *ERK1/2*, *PI3K/AKT* pathways.	Induction of cell proliferation and invasion and metastasis.	Christodoulatos et al. (2019); Spyrou et al. (2018)
Quemerin	High	It acts through the binding to receptors coupled to G proteins.	Induction of angiogenesis, inflammation and activation of *MMP*.	Christodoulatos et al. (2019); Spyrou et al. (2018)
Lipocalin 2	High	Activation of multiple signaling pathways, including *PI3K/AKT/NF-κB*, *HIF-1α/ERK* and formation of the *MMP-9/Lcn2* complex.	Promotion of EMT, migration and cell invasion.	Christodoulatos et al. (2019)
Oncostatin M (OSM)	High	It interacts with the *gp130* complex, with the type *I OSM* receptor (known as *LIFR*) or with the *OSM II* receptor (known as OSRM), stimulating several signaling pathways such as *JAK/STAT3* and *PI3K*.	Tumor progression and induction of metastasis.	Christodoulatos et al. (2019); Spyrou et al. (2018)
Osteopontin	High	Preferred binding to specific integrins, such as the *αvβ1*, *αvβ3*, *αvβe*, and *αvβ5* receptors that are associated with different signaling pathways.	Increase in adhesion, migration and cell invasion.	Christodoulatos et al. (2019)
Irisin	Low	Suppression of *NF-κB* activity.	Tumor suppression, inhibition of viability, cell migration, induction of apoptosis and decrease of inflammation.	Christodoulatos et al. (2019)
Resistin	High	It binds to *TLR4* resulting in the activation of *PI3K*, *p38 MAPK*, and *NF-κB*. Phosphorylation of the *ERM* complex (Ezrin/Radixin/Moesin).	Secretion of *TNF-α* and *IL-13*. Increase in cell proliferation, migration and cell adhesion. Resistance to chemotherapy. Promotion of ETM.	Christodoulatos et al. (2019); Spyrou et al. (2018)
RBP4 (Retinol binding protein 4)	High	Promotion of *JAK/STAT* signaling through its *STRA6* receptor.	Induction of proliferation, migration and cell invasion.	Spyrou et al. (2018)

mTOR and *p38 MAPK* signaling are involved in the apoptotic resistance and in the proliferation resulting from leptin signaling in epithelial and neutrophil cells. Given that the anti-apoptotic signaling is a common result of leptin signaling, this pathway probably has an omnipresent role in many types of cells (Figure 3) (Naylor and Petri 2016). In monocytes, leptin regulates phagocytic function through the activation of phospholipase, since it leads to the positive regulation of the surface of the Toll-like receptor (*TLR*) type 2 (*TLR2*), and since this signaling can result in the formation of lipid bodies, which is important for cell membrane formation and leukotriene production; it is possible that leptin signaling may indirectly promote phagocytosis through the induction of *TLR2*. It also promotes the expression of adhesion molecules and the secretion of pro-inflammatory cytokines (*TNF-α*, *IL-6*, e *IL-12*) (Pérez-Pérez et al. 2017).

Leptin can stimulate angiogenesis and cell cycle processes by activating the expression of the Vascular Endothelial Growth Factor (*VEGF*) and cyclin *D1*, and can inhibit apoptosis of breast cancer cells. It has been shown that the small peptide leptin receptor antagonist (*LPrA2*) decreases the growth of breast cancer in mice (Hosney et al. 2017).

Adiponectin

It is codified by the *Ad/Poq* gene and secreted by adipocytes in inverse relationship with adiposity, hyperinsulinemia and inflammation. It binds to two transmembrane receptors (*AdipoR1* and *R2*) that differ in their tissue distribution, but are often expressed in cancer cells and induce the activation of protein kinases (mainly *AMPK* and *MAPK*). Evidence points to adiponectin as an inhibitor of tumorigenesis due to its ability to activate *AMPK*, to reduce inflammation and inhibit *mTORC1* and other signaling molecules, such as insulin/*IGF-1* by inhibiting *NF-κB*, and also to exert pro-apoptotic effects by inhibiting aromatase

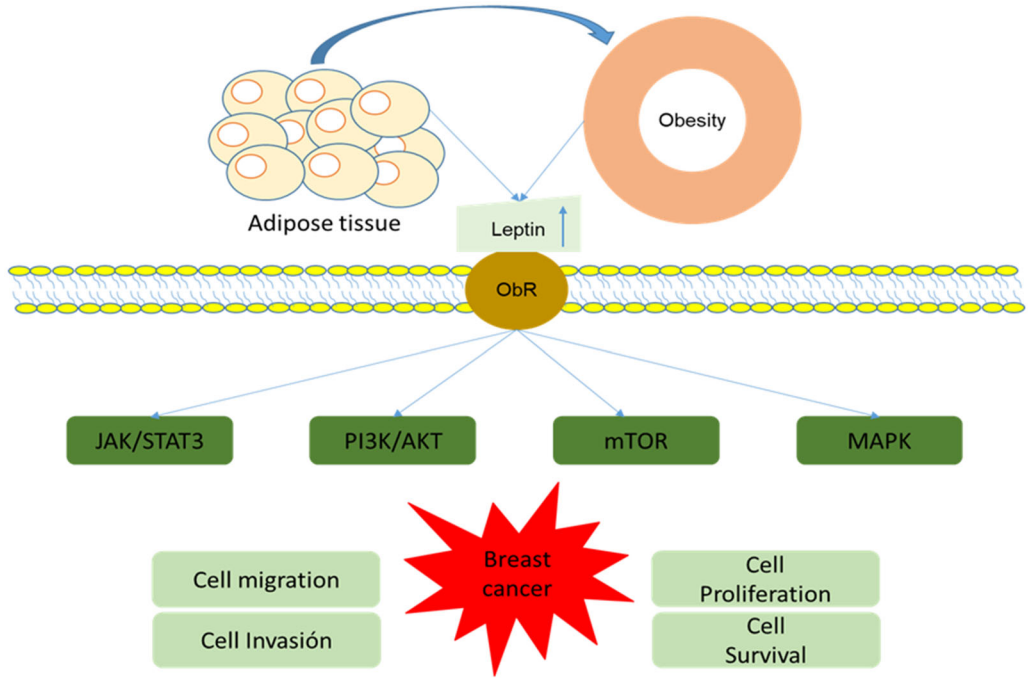

Figure 3. When there is a fatty environment in the cancer cells, there is an overexpression of leptin by the adipocytes. This adipokine acts through its receptors in breast cancer cells, positively influencing proliferation, migration, and tumor invasion. The molecular action of leptin is mediated by binding to cell surface receptors. The binding of leptin to the extracellular domain of the receptor (*ObR*) activates multiple downstream intracellular signaling pathways (including the signal transducer *JAK/STAT3*, *MAPK*, *mTOR*, and *PI3K/AKT*) that are intimately involved in apoptotic resistance. The proliferation of breast cancer cells can be the result of leptin signaling in epithelial cells and neutrophils.

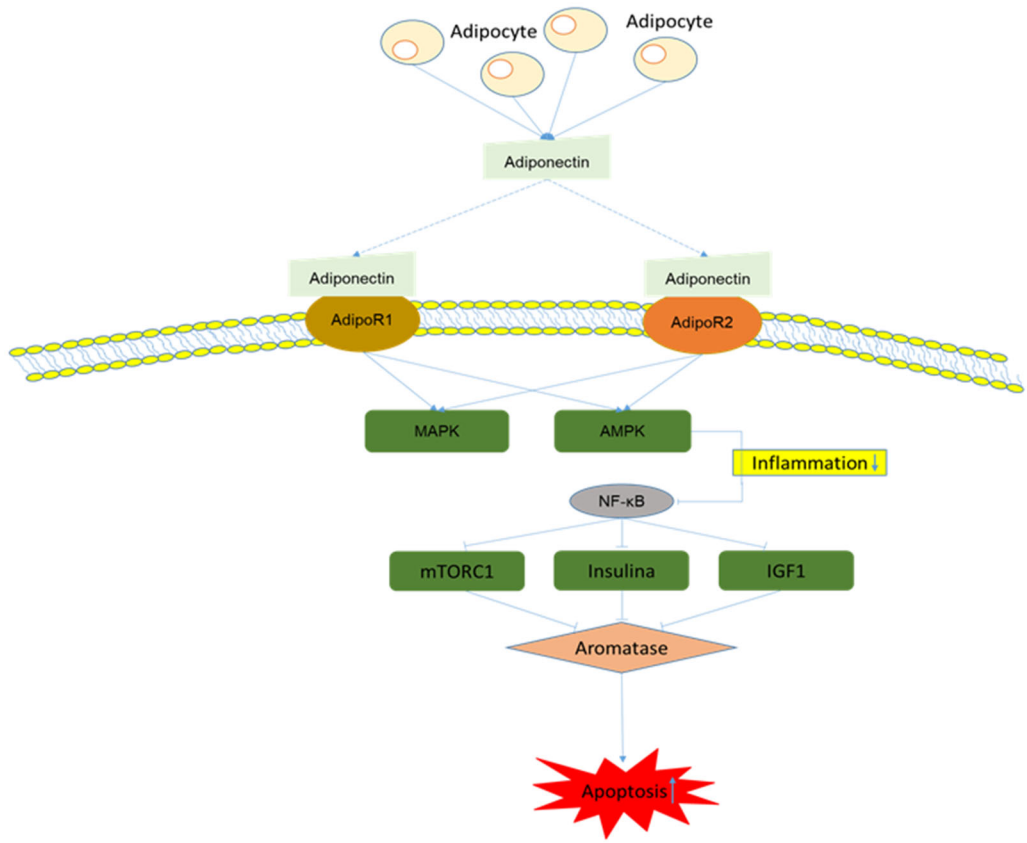

Figure 4. In breast cancer, soluble factors secreted by adipocytes, such as adiponectin, bind to their transmembrane receptors AdipoR1/2 inducing the activation of MAPK and AMPK. When AMPK is active, there is a reduction in inflammation by inhibiting NF-κB. When NF-κB is inhibited, there is no activation of mTORC1, insulin and IGF-1 and, therefore, there is no aromatase expression, so proapoptotic effects are exerted.

expression and proliferation in breast cancer cells (Figure 4). Epidemiological studies show that women with low levels of circulating adiponectin present breast tumors with more aggressive phenotypes, exemplified by a large tumor size, a high histological grade and an increased angiogenesis and metastasis (Simone et al. 2016; Sultana et al. 2017; Vucenik and Stains 2012; Font-Burgada, Sun, and Karin 2016; Dieudonne et al. 2006; Kishida, Funahashi, and Shimomura 2014).

When adiponectin binds to its receptor, it facilitates the translocation of the adaptive protein related to *LKB1/STE20* (*STRAD*)/*MO25* from the nucleus to the cytoplasm, and promotes phosphorylation of *LKB1*. Simultaneously, it activates *AMPK* which, in turn, inhibits *MAPK, PI3K/AKT, WNT-β-Catenin, NF-κB,* and *JAK2 STAT3* pathways (Christodoulatos et al. 2019; Bonan and DeCicco-Skinner 2018). Adiponectin, also inactivates *MAPK1/3* and *ERK1/2*, stimulating apoptosis by inducing the expression of *p53* and *Bax*, and decreasing the expression of anti-apoptotic proteins such as *Bcl-2* (Bonan and DeCicco-Skinner 2018).

In breast cancer cells, the effects of adiponectin depend on the state of the *ER*. In *ER-* breast cancer, it suppresses cell growth and apoptosis and inhibits proliferation, migration, and invasion. Furthermore, the results are contradictory when examining the effects on *ER+* breast cancer cells. In this type of cells, low levels of adiponectin allow the interaction of the adaptor protein, phosphotyrosine interacting with the *PH* domain and the *APPL1* with *AdipoR1, ERα, IGF-R1,* and *c-Src*. This complex activates the *AMPK* signaling pathway that promotes *ER+* breast cancer cell growth (Christodoulatos et al. 2019).

Circulating hormones and growth factors can also directly regulate the growth of tumor cells or influence tumorigenesis through modifications of the stromal microenvironment composed of fibroblasts, immunovascular cells, among others. The circulating levels of adiponectin are lower than normal in obese people with high body mass index, large subcutaneous and visceral fat areas. In obese people, the circulating adiponectin concentrations correlate inversely with the visceral fat area, but not with the body mass index nor with the large subcutaneous fat area (Kishida, Funahashi, and Shimomura 2014; Hebbard and Ranscht 2014).

Interleukins and their participation in the progression of breast cancer

Inflammation is involved in the pathogenesis of diseases associated with obesity that promote the growth of breast cancer. It has been found that the family of pro-inflammatory cytokines of *IL-1* (*IL-1α, IL-1β* and including *TNF-α*), the *IL-1* receptor antagonist (*IL-1Ra*) and receptors (*IL-1RI* and *IL-1RII*) are frequently expressed in breast cancer cell lines, in human breast cancer tissue and within the tumor microenvironment (Nicolini, Carpi, and Rossi 2006). These family members bind specific *IL-1* receptors (*IL-1R*) belonging to the *Toll-IL-1* receptor (*TIR*) superfamily, which includes 11 molecules that share an intracellular signaling domain with *TLRs*. *IL-1* may not be the only adipokine associated with breast cancer. However, it is considered an upstream adipokine, since its production (even in small amounts) induces powerful secondary responses, partly through its ability to cause the secretion of other cytokines, chemokines, adhesion molecules and receptors for cytokines of different cells (Perrier, Caldefie-Chézet, and Vasson 2009).

The *IL-1* family is mainly represented by pro-inflammatory cytokines *IL-1α* and *IL-1β* and *IL-1* receptor antagonists (*IL-1Ra*) and their receptors. There are mainly two cell surface *IL-1* receptors: *IL-1RI* (type I) and *IL-1RII* (type II), but the type I receptor with cytoplasmic domain of approximately 215 amino acids, is the only receptor responsible for the signaling of *IL-1*. Normal Human Mammary Epithelial Cells (*HMEC*) express the receptors for the members of the *IL-1* family, since *IL-1β* significantly inhibits the proliferation of *HMEC* and *IL-1ra* blocks this inhibition of growth. In addition to proliferation, *IL-1* is related to invasion, angiogenesis and the inhibition of apoptosis in cancer cells (Perrier, Caldefie-Chézet, and Vasson 2009). *IL-6* exerts its effects through the glycoprotein-mediated activation (*gp*) 130 of the signaling pathways (which include the *JAK/STAT* and *MAPK* pathways) resulting in the transcriptional regulation of the genes involved in proliferation, cell survival and differentiation; it also promotes tumor growth by positively regulating anti-apoptotic and angiogenic tumor proteins in the tumor when found in high concentrations in breast cancer cells. (Nicolini, Carpi, and Rossi 2006).

Aromatase

Aromatase, a human enzyme member of the cytochrome *P450* family, is the product of the *CYP19A1* gene, located on chromosome 15. It catalizes the limiting step of the reaction speed and the final stage of the estrogen biosynthesis; the aromatization of androgens to estrogens through three oxidation reactions of the androstenedione A ring, consuming one molecule of oxygen and *NADPH* per reaction. In postmenopausal women, the adipose tissue is the main source of aromatase and, a greater amount and/or size of adipocytes in obese patients can amplify the androgenic aromatization (Jardé et al. 2011; Iyengar et al. 2017; Chumsri et al. 2011; Morris et al. 2011; X. Wang, Simpson, and Brown 2015). It has been shown that breast cancer tissues express aromatase and produce higher levels of estrogen than non-cancerous cells (Chumsri et al. 2011). In postmenopausal women, the rate of androgen to estrogen transformation is higher in obese women (Christodoulatos et al., 2019), in addition, adipose tissue is the main source of estrogens among postmenopausal women, who do not use hormone therapy, therefore, it is not surprising that the increases in weight-related risk are often higher in women who do not use hormone therapy (Colditz and Lindsay 2018). The high risk of breast cancer associated with obesity in postmenopausal women is mainly observed in *ER+* cancer, without a history of hormone therapy, a fact that supports the hypothesis of the essential role of estrogens (Avgerinos et al. 2019).

Aromatase is a key element for the prevention and treatment of breast cancer and, it is believed that its local

expression in the WAT of the breasts promotes the growth of tumors in postmenopausal women. Inflammation of this tissue is associated with a worst prognosis for patients with breast cancer, decreased time of recurrence and overall survival (Iyengar et al. 2017).

In normal breast adipose tissue, the PI.4 promoter regulates the expression of aromatase; whereas in obesity, inflammatory mediators and cytokines such as *TNF-α* and *IL-6* stimulate the activity of the PI.4 promoter to increase the expression of the aromatase (X. Wang, Simpson, and Brown 2015), and to promote the synthesis of estrogens in postmenopausal obese women (Choi, Cha, and Koo 2018).

The excessive production of cytokines in obesity leads to the recruitment of immune cells, including macrophages derived from adipose tissue, and the formation of macrophages in *CLS* This process is accompanied by a reduced differentiation of preadipocytes and an increase in desmoplasia of ASC in the breast. The process of macrophage infiltration associated with adipocyte hypertrophy and breast inflammation also correlates positively with the BMI and adipocyte size (X. Wang, Simpson, and Brown 2015). Morris et al. (2011) determined that breast inflammation related to obesity is associated with the increase in aromatase levels (Morris et al. 2011). The death of adipocytes, caused by macrophages that form *CLS* around adipocytes, leads to the release of cellular components in the tissue, worsening the inflammation. After the cell death of these adipocytes, there is a release of FAs to the cell microenvironment, which could be used as a source of energy by the tumor cells. (Corrêa, Heyn, and Magalhaes 2019).

Excess of this enzyme can increase circulating estrogen estradiol concentrations that can cause *DNA* damage (Bonan and DeCicco-Skinner 2018; Argolo, Hudis, and Iyengar 2018). Hyperactive *ER* signaling can cause *DNA* damage by deregulating the genes that control the cell cycle, such as Cyclin *D1*. Also, they can increase the formation of *R-loops* in genes that are activated by estrogens. *R-loops* are formed when newly synthesized *RNA* binds to its *DNA* template and regulates some aspects of the transcription. The excess of *R-loops* leads to double stranded breaks in estrogen-regulated genes, which contributes to gene instability and deregulation of cell growth and proliferation (Bonan and DeCicco-Skinner 2018). By joining *ER*s, estrogens stimulate cell division, cell cycle progression, and increase proliferation and angiogenesis. *ER* activation is one of the main contributors in the progression of *ER+* breast cancer, increasing the risk of this type of cancer in postmenopausal women (Bonan and DeCicco-Skinner 2018). The increase in estrogen levels, caused by obesity, can also increase the expression of the insulin receptor A (*IR-A*), and amplify *IGF* signaling in breast cancer.

These factors contribute to the resistance of the *IGF-R1* inhibitor and the inhibition of apoptosis, respectively. In addition, estrogens can act as mitogens, activating the *MAPK* and *RTK* pathways that, like *ER*, lead to the progression, proliferation, and survival of the cell cycle (Bonan and DeCicco-Skinner 2018).

The *mRNA* levels of the enzyme in the breast tissue of 30 people were correlated with the body mass index and *CLS* in breast. Increased BMI and breast inflammation were associated with higher amounts of *mRNA* and aromatase activity. Aromatase *mRNA* levels correlate with the BMI ($r = 0.42$, $P = 0.02$) and the *CLS-B* index ($r = 0.75$, $P < 0.001$), but the correlation was stronger with the *CLS* index. Similarly, the aromatase activity correlated more strongly with the rate of *CLS* in breast ($r = 0.88$, $P < 0.001$) than BMI ($r = 0.5$, $P = 0.02$). The activation of *NF-κB* stimulates the production of several pro-inflammatory mediators that can induce aromatase. The breast samples that contained *CLS* came from overweight or obese women. The binding activity of *NF-κB* was higher in samples containing *CLS* in breast. *NF-κB* translocates to the nucleus for the transcription of *CCND1*, *c-MYC*, *JUN*, *FOS* and *Bcl-2*, regulating cell proliferation. Leptin can also induce direct activation of the estrogen receptor in *MCF-7* cells, even in the absence of its natural ligand estradiol, while, as an indirect effect, it enhances the expression of the aromatase. Leptin decreases the phosphorylation of *AMPK* and increases the nuclear translocation of the transcriptional coactivator 2 (*CRTC2*) regulated by the *cAMP* response element binding protein (*CREB*), increasing the expression of *CYP19A1* and thus, the aromatase activity (Simone et al. 2016). The increased risk of hormone receptor positive breast cancer in obese postmenopausal women has been attributed, in part, to high levels of circulating estradiol related to increased adipose tissue and to high expression of the aromatase in the subcutaneous adipose tissue (Morris et al. 2011).

Signaling pathways

Signaling pathways regulate cellular biological processes. Some inhibitors of small molecules and monoclonal antibodies are considered targeted therapies against cancer, since these agents act through disturbing signaling pathways in malignant cells (Chen and Liu 2018).

STAT3

Signal transducers and activators of transcription (*STAT*) are cytoplasmic transcription factors, which when activated by their receptors, they modify their cellular location (Hasanpourghadi, Pandurangan, and Mustafa 2018). The signal transducer and activator of transcription 3 (*STAT3*) is a crucial mediator of carcinogenesis through tumor-associated immunosuppression. Activated upstream, *STAT3* undergoes phosphorylation, homodimerization, nuclear translocation and *DNA* binding, leading to the transcription of several target genes that are involved in tumor growth, angiogenesis, invasion and immunoescape (Yu Wang et al. 2018). Moreover, it has been shown that *STAT3* is an *Hsp90* client protein that is degraded by the ubiquitin-proteasome pathway. In normal tissues, *STAT3* is widely expressed as inactive monomers in the cytoplasm. For example, after activation induced by leptin (Chang et al. 2015), *STAT3* undergoes phosphorylation at tyrosine 705 (*Tyr705*), which allows it to form homodimers, which enter the nucleus and regulate the transcription of genes involved in tumorigenesis. Phosphorylation of *STAT3* at *Tyr705* is mediated by the

activation of non-receptor tyrosine kinase proteins, including *JAK-1, JAK-2* and *Src* kinase (Figure 2) (Gupta, Phromnoi, and Aggarwal 2013). After *JAK*-mediated phosphorylation, the *STAT* proteins are dimerized and translocated to the nucleus, where they regulate gene expression. The constitutive activation of *STAT3* is associated with numerous types of cancer, and with alterations of the equilibrium state of the *JAK/STAT* pathways (in particular, signaling of *JAK2/STAT2* and *JAK1/STAT3*) producing defects in the development and contributing to breast carcinogenesis (Santillán-Benítez et al. 2014). Blocking the activity of *STAT3* by *S31-201* (*STAT3* inhibitor that blocks tyrosine phosphorylation, dimerization and DNA binding of *STAT3* in the nucleus) significantly increased the expression of *E-cadherin*, while there was a decrease in the levels of *N-cadherin* and *ZEB1* induced by leptin.

It has been found that flavonoid morin completely suppresses *STAT3* induced and activated constitutively, blocking its nuclear translocation and *DNA* binding in the multiple myeloma and in the squamous cell carcinoma of the head and neck. (Gupta, Phromnoi, and Aggarwal 2013). The flavonoid morin inhibited *Src*, activated *JAK1/2*, which are related to the activation of *STAT3*, while positively regulating *PIAS3* (protein inhibitor of activated *STAT3*). In addition, it also induced the expression of *SHP1*, both at the *mRNA* and protein levels, while the silencing of *SHP1* eliminated the effect of the flavonoid on the phosphorylation of *STAT3*, indicating that morin mediates its effects on *STAT3* through *SHP1*. In another study, Chang et al. (2015) reported how leptin regulates a transcriptional pathway to silence a genetic program of epithelial homeostasis in breast cancer stem cells that promotes malignant progression driven by obesity (induced by diet) in a murine model, where they observed that the *STAT3* blockade suppresses the *OBRhi* population of breast cancer stem–like cells (*CSC*) type and abrogates tumor progression by showing how the signaling directed to *STAT3-G9a* regulates the plasticity of *CSC* during the progression of breast cancer related to obesity, suggesting a new therapeutic paradigm to suppress *CSC* deposits and limit malignancy in the breast. When *STAT3* is activated in tumor cells, it not only cancels out the antitumor immune responses by persistently promoting *IL-6, IL-10* or *VEGF* in the tumor microenvironment, but also it transcriptionally activates the key oncogenes involved in the immune suppression involved in tumorigenesis by regulating the expression of genes involved in the proliferation of tumor cells (*C-myc, cyclin D1*), survival (*Mcl-1, Bcl-xL, survivin*), invasion (matrix metalloproteinase-9) and angiogenesis (*VEGF*) (Figure 2) (Yu Wang et al. 2018; Gupta, Phromnoi, and Aggarwal 2013; Santillán-Benítez et al. 2014).

PI3K/AKT/mTOR

The phosphoinositide-3-kinase/protein kinase B (*PI3K/AKT*) pathway integrates signals from external cellular stimuli to regulate essential functions, such as protein synthesis and glucose metabolism. However, in cancer, this pathway is deregulated, such that it becomes hyperactive, a condition that is present in approximately 30% of solid cancers, being a key event due to the prevalence of oncogenic activating mutations and the inactivation of tumor suppressor genes (for example, mutations in *PIK3R1/2*, mutations and amplifications of *PIK3CA*, amplification of *AKT1/2*, mutation in *AKT1*, loss of *PTPN1/2* and *INPP4B* and, loss and mutation of *PTEN*) (Spangle, Roberts, and Zhao 2017; O'Donnell et al. 2018). The *PI3K/AKT/mTOR* signaling pathway controls most of the characteristics of cancer such as cell cycle, survival, differentiation, proliferation, motility, metabolism and gene stability (Le Rhun et al. 2017; O'Donnell et al. 2018). The modulation of the *PI3K/AKT* pathway can also be through the regulation of *PTEN* gene activation. At the gene level, mutations that affect this gene are found in a variety of tumors such as melanoma, glioblastoma, and lung, breast, prostate, kidney, and endometrial cancers. Many types of cancer, such as prostate, lung and breast, show a reduced expression of *PTEN,* and consequently a constitutive activation of *AKT*. The regulation of *AKT* and *PTEN* is also associated with the signaling pathway of the Notch receptor. This is particularly important, since not only Notch can directly regulate the *PTEN* gene, but also the *mTOR* pathway that crosses with *AKT* (Follo et al. 2015). Likewise, activation of the *PI3K/AKT* pathway occurs in more than 50% of neoplasms, most commonly through mutational activation of the *PIK3CA* gene, mutational activation or amplification of *AKT1, AKT2* or *AKT3* or the functional loss of the lipid phosphatase *PTEN*, whose function counteracts that of *PI3K* (Spangle et al. 2016). Evidence shows that patients with haploinsufficiency of *PTEN* (associated with increased signaling of *PI3K/AKT/mTOR* downstream of the insulin receptor) not only have a higher risk of cancer compared to those who do not have this gene aberration, but rather they tend to be hypersensitive to insulin and develop obesity, suggesting that *PTEN* deficiency or overexpression of insulin are related to cancer risk. This suggests that if obesity leads to a state of insulin resistance, the inhibition of *PI3K* can prevent obesity and, therefore, *PI3K* signaling is involved in both the development of cancer and obesity (Klil-Drori, Azoulay, and Pollak 2017). In some types of cancer, insulin receptors or the *IGR* family are key activators of the *PI3K* pathway, but this pathway is most commonly activated by oncogenic events such as loss of *PTEN* function, overexpression of *HER2*, activation of mutations in *PI3K* (Klil-Drori, Azoulay, and Pollak 2017). The lipid signals *PtdIns* (3, 4, 5) *P3* (*PIP3*) and *PtdIns* (3, 4) *P2* (*PIP2*), generated by *PI3K*, are necessary for the activation of the *AKT* proto-oncogene. *PtdIns* (3, 4, 5) *P3* (second messenger), present in the membrane, activates downstream signaling pathways, many of which are divergent from *AKT*. Both *PIP2* and *PIP3* bind directly to the homologous domain of pleckstrin (*PH*) of *AKT, mTORC2* and phosphoinositide-dependent kinase 1 (*PDK1*) and the interaction of *PDK1* or *mTORC2* with *AKT* can trigger its activation, which promotes the progression of the cell cycle by regulating the synthesis of glycogen kinase 3β (*GSK3*β) and downstream cyclin *D1*. Subsequently, *AKT* activates *mTORC1*, by promoting protein synthesis and cell growth (Spangle et al

2016, Dey, De, and Leyland-Jones 2017, O'Donnell et al. 2018, Zhao, Qiu, and Kong 2017). *AKT* regulates chemoresistance through *PED* (anti-apoptotic molecule), and the phosphorylation of *AKT* in *Ser473* promotes metastasis in breast cancer. Nevertheless, patients with breast cancer who have *AKT* phosphorylated in *Ser473* appear to be sensitive to treatment with paclitaxel (Xu et al. 2018).

Another form of activation of the *PI3K/AKT/mTOR* pathway in breast cancer is the activation of *PI3K* mutations by different mechanisms, including somatic activating mutation (for example, *PIK3CA, PIK3R1*) or amplification of genes encoding key components (for example, *PIK3CA, AKT*) and amplification/overexpression of upstream tyrosine kinase receptor (for example, *IGFR1, HER2*) (Dey, De, and Leyland-Jones 2017). *PI3K* mutations are the most common genomic alterations in *ER+* breast cancer, and a positive regulation of this pathway is frequently observed in breast cancer cells devoid of estrogen in the long term. The activating mutation of *PIK3CA* is more common (~42%) in breast cancer luminal type *ER+* and, often, they match with two alterations in the number of copies (gain of *1q* and loss of *16q*) that define a present genetic signature in low-grade/luminal A breast cancer, and high-grade/luminal B (Dey, De, and Leyland-Jones 2017). *mTOR* is a serine/threonine kinase that is an inhibitor of *AKT* affinity playing a critical role in the regulation of cell growth and proliferation. In mammals, there are two structurally similar but functionally distinct *mTOR* complexes: *mTORC1* and *mTORC2*. *mTORC1* is the target of rapamycin, and rapamycin analogs such as everolimus. This complex is defined by three main components, *mTOR,* Raptor (regulatory protein associated with *mTOR*) and *mLST8*. Activation of *mTOR* leads to anabolic cell growth promoting *mRNA* translocation, protein synthesis, glucose metabolism, lipid synthesis and other anabolic processes. In addition, *mTORC1* and *AMPK* play a central role in maintaining the energy balance (Dey, De, and Leyland-Jones 2017, Saxton and Sabatini 2017, Leibovitch and Topisirovic 2017, Lindqvist et al., 2018). Energy depletion resulting in an increase of the *AMP/ATP* ratio and hypoxia reduce the activity of *mTORC1* through the *AMP*-activated protein kinase (*AMPK*) regulated in the development and *DNA* damage responses (*REDD1*), respectively (Leibovitch and Topisirovic 2017). The *mTORC2* complex includes *Rictor* (rapamycin-insensitive protein of *mTOR*), an unrelated protein that probably fulfills an analogous function, and *DEPTOR* (protein domain), as well as the regulatory subunits *mSin1* and *Protor1/2*. This complex regulates the phosphorylation of *AKT* in *Ser473* and organizes the cellular actin of the cytoskeleton. Rapalogues exert their effect mainly on *mTORC1*, and incomplete inhibition can lead to feedback loops that trigger the paradoxical activation of *AKT* to orchestrate proliferative effects through downstream targets (Saxton and Sabatini 2017; Dey, De, and Leyland-Jones 2017). *mTORC2* signaling is also involved in cancer, in large part due to its role in the activation of *AKT*, which drives proliferative processes, such as glucose uptake 1AZ and glycolysis, while inhibiting apoptosis (Saxton and Sabatini 2017).

Autophagy

Autophagy is a complex and physiological mechanism dedicated to degrade and recycle cytosolic components and damaged organelles. Proteins and organelles are first phagocytosed by autophagosomes, then digested by lysosomes, and finally recycled to be used during cell metabolism. This mechanism is involved in the generation of amino acids, it is also responsible for the replacement of cellular components that are sequestered in double-membrane vesicles, called autophagosome, which originates from a precursor structure called phagophore, where acid hydrolases are capable to degrade and recycle its charge to maintain cellular homeostasis, including cell survival and the balance of cell death (Russo and Russo 2018; Moosavi et al. 2018; Zhou et al. 2017). The activation of the signaling pathway of *mTORC1* induces anabolic processes such as the synthesis of lipids and proteins, stimulates glycolysis and inhibits autophagy, thus, promoting cell growth and proliferation (Leibovitch and Topisirovic 2017, Ben-Sahra and Manning 2017).

Given the important role of autophagy in cellular homeostasis, it is not surprising that the dysregulation of autophagy is related to multiple disease states, such as cancer. (Kimmelman and White 2017). In both normal and malignant cells, autophagy is induced by certain cell tensions in order to preserve cell survival, but if the stress is not resolved, autophagy eventually leads to programed cell death. In the early oncogenic process, autophagy acts as a tumor suppressor, preventing cellular transformation by maintaining genetic stability and modulation of reactive oxygen species (*ROS*) (Moosavi et al., 2018) to preserve cellular homeostasis, since Redox dysregulations or autophagy are associated with the beginning and preservation of the tumor (Yuan et al., 2018). In the field of the modulation of autophagy in the treatment of cancer, one of the main questions is the relationship between the rate of protein degradation through autophagy and its susceptibility when undergoing apoptosis (Bhat et al., 2018). The possible synergistic effect of estrogens and leptin in the development of breast cancer, reveals that *ER* signaling promotes leptin-induced autophagy, which in turn contributes to the growth of this cancer (Christodoulatos et al. 2019).

Effect of flavonoids on obesity and cancer

The effect of flavonoids on obesity is to improve insulin sensitivity, increase cHDL levels, reduce blood pressure and inflammatory status, in addition to modulating the expression of genes involved in lipolysis-adipogenesis and inflammation, to mention the most studied (Rabadan-Chávez et al. 2016; Grasa-López et al. 2016).

The effects of flavonoids on different types of cancer have been reported in vitro, mainly in (2 D) monolayer cell culture; however, modeling cancer complexity by using cell lines on standard plastic substrates does not respond to cancer compounds/therapies, in a similar way to real-life tissue cells, which grow three-dimensionally, unlike three-dimensional cultures (3 D), which summarize more

accurately the architecture and biology of the human solid tumor (Knight and Przyborski 2015; Lovitt, Shelper, and Avery, 2014; Sant and Johnston 2017; Imamura et al. 2015), and they are the less studied along with the murine models. To date, in clinical trials there are three polyphenolic compounds (genistein, silibinin, and resveratrol) in phases I and II, but none of them in breast cancer (Abbaszadeh, Keikhaei, and Mottaghi 2019).

Flavonoids have effects on apoptosis, cell cycle, and angiogenesis in cancer. Apoptosis is regulated through both extrinsic and intrinsic signaling pathways. In the first one, they act as ligands of the death receptors, acting on the activation of Caspase 8. By the intrinsic pathway, they increase mitochondrial ROS, increasing the release of cytochrome c, leading to the formation of the apoptosome, and consequently, caspase 9 activation, and therefore, induce apoptosis. Another way on which polyphenols generally act is by increasing the tumor suppressor genes *p53* and *p21*, inhibiting the *CDK4*/*6*-Cyclin *D* complex resulting in the cell cycle arrest (Abbaszadeh et al., 2019). Additionally, hesperetin, naringenin, and apigenin are potent aromatase inhibitors (Ye et al. 2012).

Likewise, it has been observed that intentional weight loss is related to a lower risk, particularly in cancer associated with obesity in women, highlighting the relationship between excess weight and the risk of cancer (Avgerinos et al. 2019), therefore, bariatric surgery has been linked to the reduction of cancer risk through modulation of the adipokine profile, especially with the increase in adiponectin and decrease in leptin, resistin, eNampt, and chemerin (Spyrou et al. 2018). In addition to this, weight loss can increase the browning process of the subcutaneous WAT, having an impact on the tumor microenvironment, since it can have a therapeutic effect against cancer (Corrêa, Heyn, and Magalhaes 2019).

Therapeutic effects of different flavonoids in breast cancer

Available treatments against breast cancer include chemotherapy, radiotherapy, hormone therapy, monoclonal antibodies and/or surgeries (such as lumpectomy and mastectomy). However, resistance to medications and their side effects have diminished the potential of these treatment strategies. Moreover, *TNBC* has shown resistance against hormonal treatments (Iqbal et al., 2018). Chemoprevention is the use of a natural or synthetic chemical compound to prevent, hinder, stop or revert a disease (Pan et al 2013), and since bioactive compounds of natural origin have preventive effects against cancer, there is a growing interest in using them as potential therapies against cancer. Several bioactive compounds have been studied in different stages of carcinogenesis, such as the initiation, transformation, proliferation, invasion, metastasis and angiogenesis (Srivastava et al., 2013). There are more than 250,000 species of plants and about 400 new natural products are discovered each year (Hasanpourghadi, Pandurangan, and Mustafa 2018), among which are the flavonoids, polyphenolic compounds, found in different fruits and vegetables. Chemically, flavonoids are divided into six subclasses with various biological activities including antioxidants, anti-inflammatory, anti-diabetic, anti-obesity and anti-cancer. It has been reported that flavonoids affect several pathways that lead to cell death. Some of the chemopreventive and chemotherapeutic mechanisms of these natural bioactive compounds, are that they act on the regulation of the redox state, signal transduction, modulation of gene expression involved in the suppression of inflammation, regulation of cell proliferation, differentiation, cell cycle, cell death and suppression of angiogenesis, metastasis and, therefore, the inhibition of carcinogenesis (Pan et al., 2013; Hasanpourghadi, Pandurangan, and Mustafa 2018; Moosavi et al., 2018).

Table 2 shows the effect of some flavonoids on different breast cancer cell lines (Table 1). It has been demonstrated that the cell line *MCF-7* breast cancer cells resistant to tamoxifen (selective estrogen receptor modulator) treated with 200 µM of naringenin and U0126 (*MAPK* inhibitor), showed a synergistic effect affecting the proliferation and cell viability (Eanes and Patel 2016), possibly due to the binding of naringenin to the *ER*.

Futhermore, treatment with naringenin (250 µM), besides inhibiting the *PI3K* and *MAPK* pathways, decreasing the levels of *ERK1/2* and *AKT*, induces apoptosis, resulting in a pattern of perinuclear localization of *ERα* in this type of cells. In other words, the reduction in *ERK1/2* and *AKT* levels, as well as the *ERα* levels in the nucleus of tamoxifen-resistant cells, may explain the decrease in cell proliferation/survival (Ramos et al., 2017). In *MDA-MB-231* cells, Nguyen et al. (2017) evaluated the anticancer effect of quercetin (20 µM), whose reduction in cell viability was time/dose-dependent, with inhibition of cell cycle progression, increasing expression of *FasL mRNA* and the signaling of *p51, p21* and *GADD45*. At molecular level, the natural products of plants can modulate the activities of transcription factors (such as, *NF-kB, AP-1, STAT3*), anti-apoptotic proteins (such as, *AKT, Bcl-2, Bcl-XL*), apoptotic proteins (such as, caspases and *PARP*), protein kinases (such as, *EGFR, HER2, JNK, ERK* and *p38*) and cell cycle proteins (such as, cyclins and *CDKs*) (Lewinska et al. 2017).

Therapeutic effect of flavonoids in different types of cancer

The mechanisms of action under which flavonoids exert their beneficial effects in the fight against cancer are diverse. Since the common denominator of chronic-degenerative diseases is oxidative stress, one of the most known mechanisms of action of the flavonoids is related to the increase in antioxidant status, increase in the expression of antioxidant genes and proteins. *ROS* trigger redox-sensitive species, such as apoptosis signal-regulating kinase 1 (*ASK1*), which activates downstream *MAPKs, NF-κB*, and *AP-1*, which in turn induces pro-inflammatory gene expression. Flavonoids with their strong antioxidant capacity inactivate *ROS* and other free radicals, thus preventing oxidative stress and inflammation (Ramirez-Higuera et al. 2014; Chuang and McIntosh, 2011).

Table 2. Effect of flavonoids on breast cancer cell lines

Compound	Cell line	Concentration	Biologic effect	References
Naringenin	*MCF-7*	200 μM	Inhibition of cell viability. It affects the MAPK signaling pathway. Inhibits the phosphorylation of ERK1/2.	Eanes and Patel (2016)
		250 μM	Inhibition of cell proliferation and apoptosis induction.	Ramos et al. (2017)
	E0771 (Murine breast cancer)	50, 100, and 200 μM	Reduction of cell viability and apoptosis promotion. Increases phosphorylation of AMPK and reduces the expression of Cyclin D1.	Ke et al. (2017)
	MDA-MB-231 *MDA-MD-468* *BT-549*	200 μM	Inhibition of cell proliferation and arrest of the cell cycle in the G1 phase, increase of p21 and decrease in the expression of survivin inhibiting the β-catenin pathway	Li et al. (2013)
Quercetin	*MCF-7 MDA-MB-231*	1274 μM 1442 μM	Cell arrest in phase G0/G1 in MCF-7 and in phase G2/M in MDA-MB-231	Shedid et al. 2017
	MDA-MB-231 MDA-MB-157	230 μM 415 μM	Induction of apoptosis by activation of caspase-3 and reduction of nuclear accumulation of β-catenin in both cell lines.	Sultan et al. (2017)
	MDA-MB-231	20 μM	Apoptosis and arrest of the cell cycle in the G2/M phase. The expression of FasL mRNA and the signaling activities of p51, p21 and GADD45 was increased. The transcriptional activity and nuclear translocation of Foxo3a was also induced at the protein level.	Nguyen et al. (2017)
Rutin	*MDA-MB-231*	20 y 50 μM	Arresting the cell cycle in phases G2/M and G0/G1 promoting apoptosis. Likewise, resistance to drugs is reversed by non-selective inhibition of the Pgp and BCRP pumps, achieving the reestablishment of sensitivity to cyclophosphamide.	Iriti et al. (2017)
Kaempferol	*MCF-7*	50 μM	It regulates the expression of cyclin D1, cyclin E and p21, inhibiting the progression of the cell cycle and stimulates the arrest of the cell cycle.	Kim, Hwang, and Choi (2016)
Hesperidin	*MCF-7*	11 μM	Decreased expression of Pgp levels	Febriansah et al. (2014)
		80 μM	Induction of apoptosis by the expression of caspase-3. DNA fragmentation, accumulation of suppressor gene p53.	Natarajan et al. (2011)
	MCF-7 (resistant to doxorubicin)	11 μM 50–100 μM	Inhibition of Pgp (P-glycoprotein) expressed by the multidrug resistance gene 1 (MDR1).	Febriansah et al. (2014)
	MCF-7 *MCF-7 Athymic mice* Brest cancer xenograft tumor	1–100 μM 500–5000 ppm	Increase % G_2/M Increase Go/G_1, decrease %S; reduce cyclins D, E; reduce CDK2, CDK4, no effect CDK6. Increase p21, p27, No effects p16, p18, p47 Reduce cyclin D1, no effect cyclins A,E; reduce CKD4; increase p57; no effect p21	Ferreira de Oliveira et al. (2019) Ferreira de Oliveira et al. (2019) Ferreira de Oliveira et al. (2019)
Morin	*MDA-MB-231*	50 μM	Reduction of N-cadherin expression and inhibition of AKT pathway activation.	Jin et al. (2014)
	T47D SKBR3	10 μM	Induction of apoptosis by activation of caspases-3 and -7.	Naso et al. (2013)
Myricetin	*MDA-MB.231*	5 μM	Inhibition of migration, invasion and cell adhesion. Reduction in the activity of MMP-1 and MMP-9	Ci et al. (2018)
Phloretin	*MDA-MB-231*	10–150 μM	Arrest of the cell cycle by the expression of p53 suppressor gene. Inhibition of Paxilin/Fak, Src and α-sMa through the activation of E-cadherin, achieving a decrease in the migration of cells.	Wu et al. (2018)
Luteolin	*Hs578T*	28 μM	Induction of the expression of the target genes of FOXO3a including inhibitors of cyclin dependent p21 and p27 kinases by inhibiting the PI3K/AKT pathway that subsequently increased the levels of PARP and cytochrome C, causing apoptosis and induction of cell cycle arrest in the sub-G1 phase	Lin et al. (2015)
	MDA-MB-231	27 μM		
	MCF-7	43 μM		
Flavone	*Hs578T*	55 μM		
	MDA-MB-231	44 μM		
	MCF-7	88 μM		
Apigenin	*Hs578T*	45 μM		
	MDA-MB-231	28 μM		
	MCF-7	30 μM		
Diosmin	*MCF-7*	5, 10 y 20 μM	Induction of oxidative stress and DNA damage resulting in cytostatic (5 and 10 μM) and cytotoxic (20 μM) autophagy accompanied by senescence and apoptosis.	Lewinska et al. (2017)

Obesity is strongly associated with endoplasmic reticulum stress and inflammation, such that, said stress activates protein unfolding as a response, which in turn activates three endoplasmic reticulum proteins associated with the membrane. Kaempferol (10 μM) and quercetin (25–150 μM) decrease endoplasmic reticulum stress, blocking the protein

kinase *RNA*-like endoplasmic reticular kinase (*PERK*) that mediates the phosphorylation of the eukaryotic initiation factor (*eIF2α*), the inositol-requiring enzyme (*IRE1*) that mediates the activation of the *X-box* binding protein, and the expression of the cyclic *AMP*-dependent transcription factor *ATF-6 alpha* (Chuang and McIntosh, 2011). Nevertheless, to date, studies on the mechanisms of action of flavonoids on the inhibition of endoplasmic reticulum stress are still scarce.

Both *IR* and obesity inflammation are modulated by flavonoids, for example, quercetin (3-60 μM) decreases *TNF-α*-mediated inflammation and *IR* in human primary adipocytes blocking the activation of *ERK, JNK*, *NF-κB,* and *AP-1* signaling pathways, which increases the expression of inflammatory genes such as *TNF-α, IL-6, -8, -1β,* and *MCP-1*, as well as inhibits the signaling of negative insulin regulators (*PTP)-1B* (protein tyrosine phosphatase). Inflammation and *IR* in adipocytes is also attenuated by the increase in the activation of *PPARγ* (Chuang and McIntosh, 2011).

Luteolin inhibits *CCID*, the increase in calcium induced by *MMP-1*, and the phosphorylation of *FAK*, necessary for the activation of *FAK* produced by breast cancer cells. The effect was higher, specifically on *MMP-1*, attenuating the release of cellular calcium. The combination of luteolin and quercetin, decreased the expression of *R9-nAChR*, drastically reducing cell viability in breast cancer. Similarly, the combination of paclitaxel and luteolin activated caspases and reduced the tumor, as well as the required dose of paclitaxel, and therefore, the toxicity is reduced. This chemopreventive effect was also presented with the combination with cyclophosphamide, in breast tumors induced with *DMBA*. Nevertheless, in combination with doxorubicin, the cytotoxicity of the drug is attenuated by luteolin, increasing *Bcl-2* levels and the antioxidant activity, protecting the cells from the action of the drug. Furthermore, the efficacy of luteolin was increased when it was used with rapamycin (*mTOR* inhibitor), due to the overexpression of *HER2*, because of the modulation of *p21* (Ahmed, et al., 2019).

Metformin is a first-line therapeutic agent widely used for the treatment of DM2 and currently recognized as a potential anti-cancer agent of low toxicity. Epidemiological studies have shown that the incidence of cancer in patients with DM2 treated with metformin is significantly reduced. It has been reported that co-treatment of metformin with quercetin strongly inhibited the *VEGF/AKT/PI3K* pathway in an in vivo xenographic model of prostate cancer (Sun et al., 2018). Similarly, merformin or *PPARγ* agonist, which increases adiponectin and decreases resistin and eNampt levels in both humans and mice, could be at the forefront of therapeutic strategies for malignant tumors related to obesity (Spyrou et al. 2018), in addition that it can inhibit the desmoplasia in pancreatic cancer, by reducing the remodeling of the *ECM, EMT,* and metastasis (Lengyel et al., 2018).

The combination of different chemotherapeutic agents can generate synergistic antitumor effects at lower concentrations of each of the drugs used (Sun et al., 2018). Another important factor that must be taken into account for combined chemotherapy against cancer, is the growing resistance of cancer cells to first-line drugs, which is diminished by the use of compounds, such as flavonoids, while the effect can be potentiated (Larasati et al. 2011; Baek et al. 2016; Baek et al. 2016).

Table 3 shows some of the mechanisms of action reported in cell lines of different types of cancer due to the effect of some flavonoids tested at various concentrations.

Quercetin. It has been tested against lung, prostate, cervix, esophageal and breast cancer, whose effective doses vary depending on the cell line. The most sensitive cell line was A549 of lung cancer with concentrations of 10 and 20 μM (Chuang et al. 2016), inhibiting both migration and invasion. Potentially, it reduces the expression of *PI3K/AKT* (Dutta et al., 2019).

Against prostate cancer, the IC_{50} varies from 25 and 50 μM in *PC3, DU145* and *LNCaP* cell lines (Nair et al., 2004), where it regulates the inhibition of gene expression of the *G1, S* and *G2* phases of the cell cycle, whereas in the *PC3* cell line of prostate cancer the IC_{50} ranges between 50 and 100 μM regulating the inhibition of the *β-Catenin, NF-κB* pathway and the expression of genes involved in cell migration and invasion (Senthilkumar et al. 2011). Moreover, against cervical cancer in the *HeLa* cell line, changes in cell morphology were observed with an IC_{50} of 80 μM (Vidya Priyadarsini et al., 2010), inducing mitochondrial apoptosis, releasing cytochrome C for the formation of the apoptosome, and cell cycle arrest in the *G2/M* phase was observed. In the *KYSE-510* esophageal cancer cell line, an IC_{50} of 80 μM was found, where mitochondrial apoptosis was also induced with the expression of caspase-9 and cell cycle arrest in the *G2/M* phase (Qiang Zhang, Zhao, and Wang 2009).

Naringenin. Lim et al. (2017) studied the effect of naringenin on the *PC3* and *LNCaP* cell lines of prostate cancer, with an IC_{50} of 50 μM in *PC3*, showed membrane loss and increased expression of Bax proteins, and decrease in Bcl-2, thus, activating the mitochondrial pathway of apoptosis and the decrease of phosphorylation of *ERK1/2, P70S6K* and *p38,* whereas in the *LNCaP* cell line, phosphorylation of *ERK1/2* was reduced and *p38, p53* and *JNK* were decreased.

Erdogan et al. (2017) in the *DU145, PC3* and *LNCaP* cell lines, observed induction of apoptosis by activating the mitochondrial pathway through expression of *Bax, Bid mRNA*, caspase-3, and the release of cytochrome *C, p53, p21, p27* and cell cycle arrest in the *G1* phase (150 μM). In the *SGC-7901* cell line of esophageal cancer, Bao et al. (2016) reported an IC_{50} of 40 μM where there was activation of the mitochondrial pathway of apoptosis by positive regulation of Bax and caspase-3, and inhibition of *AKT* phosphorylation. In breast cancer, Li et al. (2013) studied the *MDA-MB-231, MDA-MD-468* and *BT-549* cell lines where the *β-Catenin* pathway was inhibited and it presented cell cycle arrest in the *G1* phase at 200 μM. It has been shown that naringenin has an effect against stomach, prostate, breast ovary, lung, colon, gastric, liver, cervix, and endometrial cancer. The authors report variability in the IC_{50} from

Table 3. Mechanisms of action of flavonoids on different types of cancer.

Compound	Type of cancer	Cell line	Concentration	Mechanism	References
Quercetin	Lung	*A549*	10–20 μM	Inhibition of migration and invasion by negative regulation of MMP2 and positive regulation of expression of nm23-H1 and TIMP2	Chuang et al. (2016)
	Prostate	*PC3* *DU-145* *LNCaP*	25 and 50 μM	Regulation of the cell cycle by inhibiting the expression of genes in the G1 phase of CCND1, CCND2, CCND3, CCNE1, CCNE2, CDK2/4 and E2F2/3. From the S phase, CDK8, CDC7L1, PCNA, and CCNF specific for the G2 phase were inhibited. From the M phase, the CDC2/16 genes were inhibited. The tumor suppressor genes CBP, PTEN, MSH2, p21, ciP1, p300, HSV, BRCA1, NF2, TSC-1, TGFβR1, ALK-5 were overexpressed	Nair et al. (2004)
		PC3	50 and 100 μM	Negative regulation of uPa mRNA expression (urokinase-type plasminogen activator), EGF and their respective receptors. Inhibition of β-Catenin, NF-κB and the expression of p-EGFR, N-Ras, Ras-1, cFos, cJun and p-c-Jun. Also, the expression of mitogen-activated p38 was inhibited by inhibiting cell migration and invasion.	Senthilkumar et al. (2011)
	Cervix	*HeLa*	80 μM	Changes in cell morphology; translocation of phosphatidylserine, depolarization of mitochondrial membrane, regulation of proteins of the NF-κB family, expression of Bcl2, Cytochrome C release and apoptosome formation inducing the intrinsic pathway of apoptosis, the anti-apoptotic protein Bcl-2 and survivin were also downregulated. Arresting the cell cycle in the G2/M phase.	Vidya Priyadarsini et al. (2010)
	Esophagus	*KYSE-510*	80 μM	Activation of the intrinsic pathway of apoptosis due to increased expression of caspase-9 cleaved but not caspase-8 and cell arrest in the G2/M phase.	Zhang, Zhao, and Wang (2009)
Naringenin	Stomach	*SGC-7901*	40 μM	Induction of apoptosis by positive regulation of BAX and caspase-3, negative regulation of the antiapoptotic protein BCL-2 and surivin, and inhibition of AKT phosphorylation.	Bao et al. (2016)
	Prostate	*PC3* *LNCaP*	50 μM	In PC3, there was loss of mitochondrial membrane potential and increased expression of BAX, decreased BCL2, decreased phosphorylation of ERK1/2, P70S6K, S6 and p38. In LNCaP, phosphorylation of ERK1/2, p53, p38 and JNK decreased. In both lines, there was induction of apoptosis and generation of reactive oxygen species (ROS).	Lim et al. (2017)
		DU145 *PC3* *LNCaP*	150 μM	Induction of apoptosis by the extrinsic and intrinsic pathway by the expression of mRNA of Bax, Bid, caspase 3, cytochrome C, p53, p21 and p27, as well as decreased expression of survivin and livin in DU145 cells. Stopping the cell cycle in the G1 phase. Increased expression of the PTEN suppressor gene.	Erdogan et al. (2017)
	Breast	*MDA-MB-231* *MDA-MD-468* *BT-549*	200 μM	Inhibition of cell proliferation and arrest of the cell cycle in the G1 phase, increase of p21 and decrease in the expression of survivin inhibiting the β-catenin pathway.	Li et al. (2013)
	Ovary	*A2780*	10 μM	Activation of the extrinsic pathway of apoptosis due to increased expression of caspase-3 and activation of the stress pathway of the endoplasmic reticulum. The 153 inducible gene was also overexpressed by DNA arrest and damage.	Zhao et al. (2017)
	Lung	*A549*	50–100 μg/mL	Inhibition of migration and invasion of A549 cells, mediated by blockade of the SDF-1/CXCR-4 pathway.	Xia et al. (2018)
		MSTO-211H	160 μM	Inhibition of the expression of the transcription factor Sp1 at the level of mRNA and, modulation of the expression of the proteins asp27, p21, cyclin D1, Mcl-1 and survivin. There was regulation of the expression of Bcl-2, Bax and caspase-3, causing apoptosis.	Lee et al. (2012)
	Colon	*SNU-C4*	100 μM	Induction of specific intracellular death receptor pathways by fragmenting DNA and the formation of perinuclear apoptotic bodies. Apoptosis was induced by the expression of Bax mRNA and Caspase-3.	Park et al. (2008)

(*continued*)

Table 3. Continued.

Compound	Type of cancer	Cell line	Concentration	Mechanism	References
	Gastric	*SNU-688*	100 μM	Modulation of Bcl-2 family proteins and caspase-3 expression, showing chromatin condensation.	Park et al. (2008)
	Liver	*HepG2*	1 mM	Induction of paraptosis-like cell death by phosphorylation of mitogen-activated ERK1/2 proteins. Cytoplasmic vacuolization, mitochondrial and endoplasmic reticulum swelling as well as non-condensed chromatin were observed	Yumnam et al. (2014)
		HepG2	150 μM	The caspases −9, −8 and −3 were expressed. The Bcl-xL protein was also negatively regulated and Bax, Bak and tBid proteins were regulated positively activating the extrinsic and intrinsic pathway of apoptosis.	Banjerdpongchai et al. (2016)
	Cervix	*HeLa*	100 μM	Increase in levels of GADD153/CHOP and GRP78, endoplasmic reticulum stress proteins. ROS formation, mobilization of intracellular Ca^{2+}, and loss of the mitochondrial membrane were also promoted. Apoptosis was induced by release of cytochrome C and activation of caspase-3. Arresting the cell cycle in the G0/G1 phase by negatively regulating the expression of cyclin D1, E1 and the protein-dependent cyclin-2 kinase at the protein level.	Wang et al. (2015)
	Endometrium	*ECC-1*	50 μM	Overexpression of proapoptotic proteins Bax and Bik and decreased expression of Bcl-2 causing apoptosis. Negative regulation of the estrogen receptor-I (ESRI) that is related to the ERK/MAPK pathway.	Cincin et al. (2018)
Naringin	Stomach	*AGS*	2 mM	Induction of autophagy by suppressing the PI3K/AKT/mTOR signaling pathway through activation of MAPK	Raha et al. (2015)
	Cervix	*SiHa*	750 μM	Increased expression of caspases, p35, Bax and the FADD adapter protein of the death receptor by inducing apoptosis through the extrinsic and intrinsic pathways. Intranucleosomal DNA fragmentation and mitochondrial transmembrane potential decrease were also shown.	Ramesh and Alshatwi (2013)
	Glioblastoma	*U87 U373*	20 μM	Inhibition of activation of the MAPK pathway by reducing the expression and activity of MMP-2/9, inhibiting the invasion, migration and adhesion of U87. Reduction of ERK phosphorylation regulated by extracellular signal, p38 was also activated by mitogen and C-Jun.	Aroui et al. (2016)
Diosmin	Prostate	*DU145*	250 μM	Induction of damage to the DNA and cell chromosome, causing apoptosis.	Lewinska et al. (2015)
Phloretin	Gastric	*BGC823*	30 μM	Induction of apoptosis and decreased expression of the antiapoptotic protein Bcl-2. Induction of the PARP incision.	Lu et al. (2015)
	Esophagus	*EC-109*	60 μg/mL	Induces negative regulation of Bcl-2 antiapoptotic protein and increased levels of apoptosis-associated proteins such as protein 4 type Bcl-2 and p53. Also, the expression of factor 1 activator of the apoptotic protease was affected, activating the intrinsic pathway of apoptosis.	Duan et al. (2017)
	Colon	*HT-29* *COLO-205*	100 μM	Arresting the cell cycle in COLO205 in a p53-dependent manner.	Lin et al. (2016)
		SW620 *HCT-116* (phloretin: atorvastatin)	100:10 μM	Synergistic effect that resulted in the arrest of the cell cycle in the G2/M phase inducing apoptosis. The expression of cyclin was negatively regulated and positively the expression of phospho-cdc2 and Myt-1.	Zhou et al. (2018)
		HT-29	50 μM	Increased expression of Bax by activating the intrinsic pathway of apoptosis by increasing the regulation of cleaved caspases −8, −9, 7, −3 and PPAR. Also, there was cytochrome C release	Park et al. (2008)
	Glioblastoma	*U87 U251*	200–300 μM	Expression of p27 and diminution in the expression of CDK2/4/6, cyclin D and E associating to arrest of the cell cycle in phase G0/G1. Inhibition of PI3K/AKT/mTOR signaling pathways in a dose-dependent manner. Overexpression of proteins Bax, Bak and cPARP and negative regulation Bcl-2 triggering the activation of the intrinsic pathway of apoptosis and generating reactive oxygen species (ROS).	Liu et al. (2016)

(*continued*)

Table 3. Continued.

Compound	Type of cancer	Cell line	Concentration	Mechanism	References
	Liver	*HepG2*	50–150 mM	Induction of apoptosis by activation of caspases −3, −8 and −9.	Yang et al. (2009)
	Lung	*A549* *Calu-1* *H838* *H520*	75 μg/mL	Inhibition of Bcl-2, expression of caspases −3 and −9 and dysregulation of MMP2/9 at the gene and protein levels to induce apoptosis.	Ma et al. (2016)
		A549	200 μM	Increased expression of Bax, caspase-3 and -9 cleaved and the degraded form of PARP. Regulated negatively Bcl-2. Also, phosphorylation of p38 MAPK, ERK1/2 and JNK1/2 was activated by inhibiting the migration and induction of apoptosis.	Min et al. (2015)
Fisetin	Prostate	*LNCaP* *CWR22Ru1* *PC3*	60 μM	Arrest of the cell cycle in the G1 phase associated with a decrease in the expression of cyclin D1, D2 and E. The intrinsic pathway of apoptosis was induced by the release of cytochrome C, cleavage of PARP and modulation of Bcl-2 family proteins. Also, PI3K and AKT phosphorylation were inhibited.	N. Khan et al. (2008)
		PC3	25 μM	Increase in the expression of p21 and p27 proteins. Expression of caspase-3, Bax, cytochrome C inducing activation of the intrinsic pathway of apoptosis. There was also an increase in the expression of p21 and p27 proteins that was accompanied by apoptosis.	Erdogan et al. (2016)
		PC3 *DU145* *LNCaP*	40, 80 y 120 μM	The levels of Raptor, Rictor, PRAS40 and Gbl were reduced, inhibiting the formation of mTORC1/2 complexes inducing autophagic cell death. AKT was also inhibited and AMPK was activated.	Suh et al. (2010)
	Skin	*A375* *451Lu*	60 μM	Induction of stress of the endoplasmic reticulum by positive regulation of its markers IRE1a, XBP1s, ATFa and GRP78, associating with the activation of the extrinsic and intrinsic pathways of apoptosis	Syed et al. (2014)
	Lung	*A459* *H1792*	20 μM	Decreased protein expression of PI3K (p85 and p110), inhibition of AKT phosphorylation and constituents of the mTOR pathway (p70S6K1, eIF-4E 4E-BP1, Raptor, GβL and PRAS40). The phosphorylation of AMPKα were increased and a decrease in the phosphorylation of TSC2.	Khan et al. (2012)
Resveratrol	Lung	*H838* *H520*	50 μg/mL	Depolarization of mitochondrial membrane potential, release of cytochrome C and expression of Bcl-2 and Bax to activate the intrinsic pathway of apoptosis. The effect of cisplatin (an inhibitor of cell proliferation) was potentiated.	Ma et al. (2015)
Morin	Cervix	*HeLa*	100–500 μM	Arrest in phase G2/M. Reduction of the expression of survivin, Cdc25c, Cyclin B1, CHK2 caspases 9,10, DR3, DR5, Bcl2, AMPK, NF-κB and increase of Bax, Bad, Cytochrome c, PI3K, AKT, mTOR, p53 and p21. Induction of apoptosis by extrinsic and intrinsic pathway	Zhang et al. (2018)
Hesperidin	Adenocarcinoma	*A431*	30–200 μM	Reduce cyclin D, CDK2. Reduce % Go/G1; increase %S	Ferreira de Oliveira et al. (2019)
		A549	30–200 μM	Reduce cyclin D; Reduce % Go/G1	Ferreira de Oliveira et al. (2019)
	Biphasic mesothelioma	*MSTO-211H*	40–160 μM	Reduce cyclin D; Reduce % Go/G1, reduce p21, p27	
	Epidermoid carcinoma	*A-431*	10–500 μM	Reduce cyclin A2, B1, D1, D3, E1; increase p21	
	Squamous cell carcinoma	*Eca109*	100–300 μM	Increase Go/G_1; reduce cyclin D1, increase p21	
	Cervical adenocarcinoma	*HeLa*	40–60 μM	Increase Go/G1; Reduce cyclin D1, E1, CDK2	
	Hepatocellular carcinoma	*Hep3B*	209 μM	Reduce cyclin D1	
	Chronic myelogenous leukemia	*K562*	50–200 μM	Increase Go/G_1; reduce %S; Increase p21, p19	
	osteosarcoma	*U-2 OS*	330–450 μM	Increase G_2/M; reduce cyclin B1, E1, CDK1, CDK2	
	AOM-induced colon cancer	*Swiss albino mice*	25 mg/Kg bw	Reduce cyclin D; increase p21	
	Glioma xenograft model	*Wistar rats*	20 mg/Kg bw	Reduce cyclin B1,D1	

10 µM to 160 µM, and from 1 mM to 250 mM. The mechanism observed in the different cell lines in different types of cancer, was mainly the activation of the mitochondrial pathway of apoptosis by caspase-3 positive regulation, release of cytochrome *C* and regulation of *Bax, Bak* and *tBid*, as well as inhibition of phosphorylation of *ERK1/2, JNK, AKT* and regulation of the *MAPK* pathway; this flavonoid also causes cell cycle arrest in the *G1* phase (Table 3).

Naringin. It has an effect against stomach cancer, cervix cancer, and glioblastoma. It was found that in the *AGS* stomach cell line, there was regulation through autophagy (Raha et al., 2015), inhibiting the signaling pathway of *PI3K/AKT/mTOR* through the activation of *MAPK*. In the *U87* cell line of glioblastoma, the *MAPK* signaling pathway was inhibited, and therefore, there was a reduction in *MMP-2/9* activity, thereby inhibiting migration, invasion and cell adhesion.

Phloretin. It has an effect against cell lines of esophageal cancer, gastric cancer, colon cancer and glioblastoma. The main mechanisms proposed by the different authors is the activation of the mitochondrial pathway of apoptosis in the different cancer cell lines, with cell cycle arrest in the *G0/G1* and *G2/M* phase. In gastric cancer, colon cancer and glioblastoma an incision of poly ADP-ribose polymerase (*PARP*) that is involved in the processes of *DNA* repair and programed cell death was observed. There is inhibition of cell migration by phosphorylation of *p38, MAPK, ERK1/2* and *JNK1/2* and, therefore, there is cell death by apoptosis. In glioblastoma cancer (Liu et al., 2016) a dose-dependent inhibition of the *PI3K/AKT/mTOR* signaling pathway was observed at a concentration of 200 to 300 µM.

Fisetin. It has shown effect against prostate cancer cell lines (*LNCaP, CWR22Ru1, PC3*), skin cancer (*A173* and *451Lu*) and lung cancer (*A459* and *H1792*) finding that the IC_{50} ranges from 25 to 120 µM. The main mechanisms proposed by the authors are the induction of apoptosis by the activation of the mitochondrial pathway, cell cycle arrest in the *G1* phase, decrease of cyclins *D1/2/E*, and inhibition of the *PI3K/AKT* pathway, as well as induction of autophagy by the inhibition of *mTOR* complexes 1 and 2, and the activation of the *AMPK* pathway (Table 3). Downregulation of *ERK1/2*, *AKT*, *MAPK*, *NF-κB*, cyclin *D1*, *Bcl-2*, survivin and heat shock factor (*HSF1*), and upregulation of *p21* and *p27* (Abbaszadeh et al. 2019).

Hesperetin, naringenin, and apigenin are potent aromatase inhibitors (Ye et al. 2012), and the combination of naringenin and hesperitin inhibits the phosphorylation of focal adhesion kinases (*FAK*) and *p38* signaling, unlike when they are alone (Lee, Kim and KIm 2019).

Resveratrol. Ma et al. (2015) have reported the effect of resveratrol against the *H838* and *H529* lung cancer cell lines, with an IC_{50} of 50 µg/mL, causing apoptotic cell death through the mitochondrial pathway, as well as potentiating the effect of the reference drug, cisplatin. As anti-cancer mechanism of action, they have found negative regulation of *NF-κB, MMP-9*, survivin, cyclin *D1*, *COX2*, and *ICAM-1* (Abbaszadeh et al. 2019).

Conclusions

In the tumor microenvironment, adipokines and cytokines secreted by the adipose tissue in obese individuals influence the development and progression of breast cancer through inflammatory stimuli, angiogenesis and the expression of anti-apoptotic proteins. When there is a high secretion of leptin, there is a positive regulation of the aromatase enzyme activity that is capable of activating some signaling pathways involved in the development of breast cancer such as *PI3K/AKT/mTOR* and *STAT3*. Nowadays, in vitro and in vivo studies with natural products, mainly flavonoids, have shed more evidence about the molecular aspects of adipose tissue regulation in obesity/diabetes and its relation with breast cancer; however, there is still a lack of studies where the therapeutic target is to reduce or inhibit the overexpression of leptin, pro-inflammatory cytokines and adipokines, and at the same time increase adiponectin levels, since the latter, by positively regulating pro-apoptotic proteins, it is an alternative to decrease progression, angiogenesis, survival and development of *ER-* breast cancer. Moreover, it is also necessary to search for leptin receptor antagonists in order to decrease the aromatase expression, and thus, to inhibit the overproduction of estrogen. Nevertheless, a greater number of studies are needed to define which conditions of obesity are necessary to promote the adipose tissue browning, since the evidence points out that this process is involved in the development of cancer. Additional studies are needed to clarify when the inhibition of inflammatory processes is associated to the development and progression of cancer, or in which conditions, the oposite might be true. For example, at low levels of adiponectin, in *ER+* breast cancer, it promotes cell growth through indirect *MAPK* activation.

It is also necessary to migrate to three-dimensional cellular models that mimic the functioning of the tumor, to establish the appropriate combinations, as well as the concentrations of the compounds with the first-line drugs, since they change the response depending on the specific metabolic pathways in each case.

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