# Flavonoids in Breast Cancer

Breast cancer (BC) remains the second most common cause of cancer-related deaths in women in the US, despite advances in detection and treatment. In addition, breast cancer survivors often struggle with long-term treatment related comorbidities. Identifying novel therapies that are effective while minimizing toxicity is critical in curtailing this disease. Flavonoids, a subclass of plant polyphenols, are emerging as promising treatment options for the prevention and treatment of breast cancer. Recent evidence suggests that in addition to anti-oxidant properties, flavonoids can directly interact with proteins, making them ideal small molecules for the modulation of enzymes, transcription factors and cell surface receptors. Of particular interest is the ability of flavonoids to modulate the tumor associated macrophage function. However, clinical applications of flavonoids in cancer trials are limited. Epidemiological and smaller clinical studies have been largely hypothesis generating. Future research should aim at addressing known challenges with a broader use of preclinical models and investigating enhanced dose-delivery systems that can overcome limited bioavailability of dietary flavonoids.

## 1. Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women worldwide and the second most common cause of cancer-related mortality in women in the US [1][2]. Despite the advancement on early detection methods and intensive interventions, questions pertaining to the mechanisms underlying the aggressiveness of certain forms of cancer such as the triple negative breast cancer (TNBC) remain unanswered. Identifying additional treatments and preventive approaches continues to be critical in curtailing BC. Epidemiological studies suggest that the consumption of healthy diets, rich in fruits and vegetables, and body weight are positively associated with a reduced incidence of BC [3][4]. Flavonoids, plant polyphenols broadly present in fruits and vegetables, are emerging as promising arsenals for the prevention and treatment of cancer and other chronic inflammatory diseases [5][6][7][8][9]. Flavonoids show anti-carcinogenic, anti-metastatic and immuno-modulatory activities in cellular and preclinical animal models making them potential candidates in cancer prevention and treatment. Despite the well-established role of flavonoids as antioxidants, recent evidences show that flavonoids directly interact with proteins, making them ideal small molecules for the modulation of enzymes, transcription factors and receptors [10]. These novel properties of flavonoids propose new platforms to modulate tumor signaling, overcome chemo-resistance and re-educate the tumor microenvironment (TME). Unraveling these novel mechanisms of action of flavonoids offers great clinical opportunities.

## 2. Flavonoids: Molecular Mechanisms of Action

### 2.1. Antioxidant Effects of Flavonoids in Breast Cancer

The health benefits of the flavonoids have been historically ascribed to their chelating and antioxidant properties led by their innate chemical structure [11]. The presence of multiple hydroxyl groups along with a highly conjugated delocalized electron system enhance the free radical scavenging nature of the flavonoids and its interference with the redox activity of the cell [12]. In general, flavonoids have been shown to block the production of reactive oxygen species (ROS) in macrophages, thereby mediating their immune modulating activity [13][14][15][16].

In vitro studies on hormone sensitive ER+ human BC T47D and MCF-7 cell lines have shown that flavonoids found in wine, like quercetin and resveratrol, inhibit proliferation by antagonizing hydrogen peroxide ($H_2O_2$) [17]. Flavones possessing multiple hydroxyl groups, such as apigenin and luteolin, induced apoptosis and cell cycle arrest in MCF-7 and the TNBC cell lines through the inhibition of PI3K/Akt and increased FOXO3a (forkhead box protein) activation, which is associated with ROS reduction [18]. Butein, a tetrahydroxy chalcone, suppressed the growth of HCC70 (TNBC), BT-474 (HER2+) and T47D (ER+) human BC cell lines by reducing ROS and inducing apoptosis, as evidenced by the increased

caspase-3 and caspase-9 activities [19]. Interestingly, flavonoids can also induce ROS accumulation, depending on the cell type and culture conditions, suggesting additional mechanisms responsible for triggering cell death. The flavanone naringenin induces ROS dependent apoptosis in human MDA-MB-468 TNBC cells [20]. Myricetin can suppress the growth of MDA-MB-231 and MDA-MB-468 cell lines by activating pro-apoptotic agents via a pro-oxidant effect, which is mediated by $H_2O_2$ generation [21][22][23]. The flavone 5,7-dihydroxy, 8-nitrochrysin, exerted cytotoxicity on HER2 overexpressing MDA-MB-453 human BC cells by the generation of ROS and Akt dephosphorylation [24][25]. Silibinin, a mixture of flavanolignans, induced apoptosis in MDA-MB-231 cells through ROS-dependent Notch-1/ERK/Akt pathway and nuclear translocation of the apoptosis-inducing factor (AIF) [26]. Flavonoids can also induce apoptosis in a ROS-independent pathway. Common shortcoming in the field is that sometimes the observed changes in activities represent secondary effects that might not be necessary and/or sufficient for the biological effects exerted by the flavonoids. Illustrating this point, our group showed that the flavone apigenin induces a quick ROS production followed by caspase-3-dependent apoptosis in leukemia cells. However, we found that ROS inhibitors failed to inhibit apoptosis, clearly indicating that ROS production was dispensable for the apigenin-induced cell death [27]. Therefore, the beneficial effects of flavonoids in cellular models of BC can be due to antioxidant-dependent and independent pathways. Hence, caution on the interpretation of the results and studies devoted to a deeper dissection of the mechanisms of action are much needed in the field of flavonoids for health.

In BC xenograft mouse models, flavonoids have shown to significantly reduce cell growth through the production and scavenging of ROS. The myricetin derived flavonoid oncamex, induced increased superoxide production and cytotoxicity in MDA-MB-231 xenografts [28]. Treatment of BT-474 xenografts with butein reduced tumor growth through the reduction of ROS and induction of apoptosis [19]. Flavonoids extracted from *Radix Glycyrrhiza* attenuated tumor mass of MDA-MB-231 xenografts by the inhibition of iNOS (inducible Nitric Oxide Synthase) and inactivation of the JAK2/STAT3 signaling pathway [29]. Apigenin and luteolin inhibited intravasation mechanisms in the MDA-MB-231 breast cancer spheroids thereby hindering its growth and migration through the lymph endothelial barrier [30]. This study reveals insights into the potential effects of flavonoids to inhibit metastasis. Future studies using 3D cultures of BC cell lines and with patient derived xenografts (PDX) will be crucial for evaluating the clinical potential of flavonoids alone or in combination with chemotherapeutic drugs in BC treatment.

BC recurrence, metastasis, and the limited success of current therapies are in part ascribed to the complexity of the TME. Macrophages, key immune cells abundant in the TME, regulate tumor growth, invasion, metastasis and harbor immune-suppressive conditions [31][32]. Increased numbers of tumor associated macrophages (TAMs) in the TME and circulatory myeloid progenitors, including inflammatory monocytes (i-Mo) and myeloid derived suppressor cells (MDSCs), are responsible for defective immune-surveillance [33][34][35]. The presence of these cells has been correlated with increased metastasis and poor clinical prognosis [36]. There is also compelling evidence that TAMs limit the efficacy of chemotherapy [37][38][39][40]. Thus, the ability of flavonoids to target the macrophage function has attracted great interest as a potential approach to increase the efficacy of current standard of care and reduce the immunosuppressive conditions of the TME in BC.

We showed that the flavone apigenin exerts immunoregulatory activity in macrophages and its myeloid progenitors. Apigenin reduces the phosphorylation of p65 subunit of nuclear factor NFκB, responsible for its transcriptional activity [13]. NFκB is a key transcription factor in cancer controlling both the proliferation of cancer cells and the immune response [41]. NFκB regulates the expression of tumor necrosis factor alpha (TNFα) and interleukin-1β (IL-1β) in macrophages, whereas in tumor cells, increases the expression of anti-apoptotic molecules [42], contributing to increased resistance of cancer cell to current chemotherapies. A study involving multiple hydroflavones reported that chrysin suppressed the level of IL-1β m-RNA in LPS/IFN-γ (lipopolysaccharide/interferon gamma) activated RAW 264.7 mouse macrophages, whereas the addition of OH groups in the C ring (galanin) and B ring (quercetin and kaempferol) decreased this effect [43]. We showed that apigenin reduces TNFα and IL-1β expression in macrophages, even when added after inflammatory stimuli, suggesting its therapeutic potential [13]. Apigenin also reduces nitric oxide synthase (NOS) and cyclooxygenase (COX) expression in macrophages [44][45]. Furthermore, using transgenic NFκB-luciferase reporter mice, we showed that apigenin decreases NFκB activity in vivo [46]. Apigenin was also found to induce apoptosis in mouse macrophage ANA-1 cells through the increased ROS accumulation and high caspase-3 activity followed by activation of the mitogen-activated protein kinase (MAPK) pathway [47]. However, the concentrations used in cellular and animal models are frequently unreachable in vivo, potentially disguising the main mechanisms and clinical potential (**Table 2**). Apigenin and quercetin inhibited the expression of TNFα in peripheral blood mononuclear cells (PMBC) by halting the NFκB pathway [48][49]. Citrus flavonoid, hesperidin, reduced the ROS generation in human neutrophils and induced caspase-3-dependent apoptosis [50][51]. Flavonoids like epigallocatechin gallate (EGCG), found in green tea, can suppress human monocytic derived dendritic cells through apoptosis and the suppression of cell surface molecules and antigen presentation, suggesting its potential for immuno-therapies [52][53]. Luteolin inhibited lipopolysaccharide induced COX-2 expression and

xanthine oxidase generated superoxide in the RAW 246.7 macrophages [54]. In a study pertaining to the effect of flavonoids on macrophage activation, it was shown that flavonols with 3' and 4' hydroxylations in the B ring, as in quercetin and kaempferol, exerted the highest degree of TNFα inhibition. Whereas, flavones like apigenin, luteolin and diosmetin were more effective in suppressing the NO and IL-1β production when compared to the flavonols [55][56]. Overall, these findings suggest that flavonoids can affect tumors and its metastases by affecting other components of the TME ecosystem.

**Table 2.** Flavonoid doses in different experimental models.

| Study Type | Experimental Model | Treatments | Dose | Results | Reference |
|---|---|---|---|---|---|
| Cellular Studies | T47D and MCF-7 | Wine polyphenols | 1 pM–100 nM | Inhibited growth and antagonize $H_2O_2$ | [17] |
| | HCC70, BT-474 and T47D | Butein | 0.001–100 µg/mL | Induced apoptosis through ROS reduction | [19] |
| | MDA-MB-468 | Naringenin | 2.5–50 µM | Oxidative stress induced apoptosis | [20] |
| | MDA-MB-231 and MDA-MB-468 | Myricetin | 20–100 µM | Oxidative stress induced apoptosis | [21] |
| | MDA-MB-453 | 5,7-dihydroxy, 8-nitrochrysin | 2–8 µM | Induced apoptosis by generation of ROS | [24] |
| | MDA-MB-231 | Silibinin | 30 µM | Induced apoptosis | [25] |
| | Human monocytes and RAW 264.7 | Apigenin | 0.1–25 µM | Reduced NFκB phosphorylation, TNF-α and IL-1β expression | [13] |
| | RAW 264.7 | Chrysin | 30 µM | Suppression IL-1β expression | [43] |
| | RAW 264.7 | Apigenin | 10–25 µM | Reduced NOS and COX expression | [44] |
| | ANA-1 | Apigenin | 12.5–200 µM | Induced apoptosis | [45] |
| | Human PBMC | Quercetin | 1–50 µM | Inhibited TNF-α expression | [48] |
| | Human Neutrophils | Hesperidin | 1–100 µM | Reduced ROS generation and induced apoptosis | [51] |
| | Human Dendritic cells | EGCG | 10–100 µM | Induced apoptosis | [53] |
| | RAW 264.7 | Luteolin | 25–100 µM | Inhibited COX-2 and xanthine oxidase expression | [54] |
| | Bone marrow derived mouse macrophages | Quercetin and Kaempferol | 25–50 µM | Inhibited TNF-α expression | [56] |
| | MCF-7 | Apigenin and Chrysin | 10–50 µM | BCRP inhibitors | [57] |
| | MCF-7 and T47D | Methoxyflavones from *Tanacetum gracile* | 1.5–5 µM | Induced cell cycle arrest through tubulin binding | [58] |
| | MDA-MB-231 | Apigenin | 25 µM | Inhibited hnRNPA2 dimerization affecting its splicing activity | [59] |
| | MCF-7 | Apigenin | 25–100 µM | Suppressed MUC-1 expression and induced apoptosis | [60] |

| Study Type | Experimental Model | Treatments | Dose | Results | Reference |
|---|---|---|---|---|---|
| Cellular Study | CD4 T cells | Apigenin | 12.5–75 µM | Potentiated activation induced cell death by suppressing NFκB regulated anti-apoptotic pathways | [61] |
| | Dendritic cells | Quercetin | 50 µM | Attenuated LPS induced DC activation | [62] |
| | MCF-7 | Apigenin | 20–80 µM | Reduced cell growth and expression of MDR1 and P-gp in MCF-7-doxorubicin resistant cells | [63] |
| | MCF-7, MDA-MB-231 and HMF | Rutin | 20 µM | Increased the cytotoxicity of cyclophosphamide and methotrexate | [64] |
| | MDA-MB-231 | EGCG | 10–25 µM | Synergistic enhancement of cytotoxicity with tamoxifen | [65] |
| | MCF-7 | Resveratrol | 50–250 µM | Increased sensitivity to doxorubicin | [40] |
| | MDA-MB-231 and MCF-7 | Resveratrol | 80–180 µM | Synergistic inhibition of growth with doxorubicin | [66] |
| | MCF-7 | Apigenin | 30 µM | Enhanced cisplatin cytotoxic activity | [67] |
| | BT-474 and SK-BR3 | Flavopiridol | 50–100 nM | Synergistic inhibition of cell proliferation with trastuzumab | [68] |
| | MDA-MB-231, MDA-MB-468 and SK-BR3 | Flavopiridol | 0.2 µM | Enhanced sorafenib induced cytotoxicity | [69] |
| | BT47D and MDA-MB-231 | Apigenin | 10–80 µM | Induced apoptosis and autophagy | [70] |
| | MDA-MB-231 | Wogonin | 50–100 µM | Sensitized TRAIL-induced apoptosis | [71] |
| | RAW 264.7 macrophages and 3T3-L1 adipocytes co-culture | Luteolin | 1–20 µM | Suppressed the adipocyte-dependent activation ofmacrophage | [72] |
| 3D Study | MDA-MB-231 | Apigenin and Luteolin | 20 µM | Attenuate growth and intravasation through endothelial barrier | [30] |

| Study Type | Experimental Model | Treatments | Dose | Results | Reference |
|---|---|---|---|---|---|
| Animal Study | BALB/C-Tg (NFκB-RE-luc)-Xen mice | Apigenin | 50 mg/kg body weight | Reduced NFκB activity in lungs in vivo | [46] |
| | CD-1 immunodeficient mice bearing MDA-MB-231 tumor | Oncamex | 25 mg/kg body weight | Inhibited tumor growth | [28] |
| | Athymic nu/nu nude mice bearing MDA-MB-231 tumors | Radix Glycyrrhiza extracts | 20–100 mg/kg body weight | Attenuated tumor growth through iNOS inhibition | [29] |
| | C57BL/6 mice | Luteolin | HFD with 0.01% luteolin | Inhibited inflammatory macrophage polarization in adipose tissue | [73] |
| | C57BL/6 mice | Quercetin | HFD with 0.1% luteolin | Attenuated macrophage recruitment and modulated M1/M2 macrophage ratio | [74] |
| | BALB/c mice bearing 4T1 tumors | Quercetin | 5mg/kg body weight | Synergistic inhibition of tumor growth with doxorubicin | [75] |
| | Athymic nu/nu nude mice bearing BT47D tumors | Apigenin | 50 mg/kg body weight | Inhibited the progression progestin dependent BT-474 xenograft tumors in nude mice through apoptosis | [76] |
| | Athymic nu/nu nude mice bearing MDA-MB-231 tumors | Apigenin | 25–50 mg/kg body weight | Inhibited tumor proliferation and proteasome activity | [77] |
| | Ovariectomized C57BL/6 mice injected with E0771 cells | Naringenin | HFD with 1–3% naringenin | Reduced adipose tissue mass and ameliorated adipose tissue inflammation | [78] |
| | C57BL/6 mice | *Hippophae rhamnoides* L. seeds extracts | 100–300 mg/kg body weight | Significant anti-obesity and anti-inflammatory effect | [79] |
| | Ovariectomized female C57BL/6 mice | Resveratrol | 300–600 mg/kg body weight | Inhibited obesity-associated increases in claudin-low mammary tumor growth and macrophage infiltration | [80] |

BRCP: Breast cancer receptor protein; hnRNPA2: heterogeneous nuclear ribonuclear protein A2; MUC-1: Mucin-1; DC: Dendritic cells; MDR1: Multidrug resistance 1; P-gp: P-glycoprotein; TRAIL: TNF-related apoptosis-inducing ligand; HFD: High fat diet.

**2.2. Flavonoid-Protein Interactions as Regulators of Breast Cancer**

Recent studies provide evidences that flavonoids can also exert their functions by targeting proteins directly. Their structural resemblance to certain estrogens is responsible for the ability of isoflavones (e.g., genistein) and flavanone (e.g., naringenin) to bind to the nuclear estrogen receptors ERα and ERβ [81]. Their increased affinity for ER relies on the 7-OH of A ring and 4′-OH of B ring. However, glycosylated flavonoids like naringenin-7-*O*-glucoside have weaker affinity for ER. Flavonoids have also been found to act as competitive inhibitors of drug transporters, including the breast cancer receptor protein (BCRP) and the ABC transporters P-glycoprotein (P-gp) and multidrug resistance-associated proteins (MRP1 and MRP2) [82][83][84]. Structural based studies of flavonoids on MCF-7 cell lines resistant to the antineoplastic antibiotic mitoxantrone found that apigenin and chrysin increased the accumulation of mitoxantrone in BRCP overexpressing the MCF-7 cells [57]. Similar studies have confirmed the high inhibitory activity of *O*- and *C*-methoxylated flavonoids, such as retusin and ayanin, in MCF-7 BRCP overexpressing cells, underscoring the potential role of the methyl groups in targeting proteins [82][85]. The ability of flavonoids to induce the cell cycle arrest can be attributed to the interaction of its different functional groups with cyclin dependent kinases (CDKs). Molecular dynamic simulations to understand the binding behavior of flavonoids that inhibit CDK6/cyclin D complex showed that hydroxyl groups at 3′ and 4′ positions of B ring (e.g., luteolin) are favorable for the hydrogen bond formation with CDK6/cyclin D, in contrast to the 3-OH on the C ring found in galangin and the 5-OH found in the A ring of chrysin [86]. Apigenin induced G2/M cell cycle arrest in MCF-7 and MDA-MB-468 cell lines by modulating CDK1/cyclin B1 complex accompanied by ERK/MAPK inhibition [87]. Biochemical and molecular docking studies suggested that some methoxyflavones from *Tanacetum gracile* induce cell cycle arrest in MCF-7 and T47D through the direct binding of tubulin [58][88].

The novel approach PD-Seq (phage display coupled with second generation sequencing), that combines the phage display with next generation sequencing, identified 160 direct targets of apigenin from more than 15,000 proteins represented in a human breast cancer library [59]. Notably, in this study our group identified that the top candidate directly interacting with high affinity to apigenin is the heterogeneous ribonuclear protein A2 (hnRNPA2). HnRNPA2 is a RNA binding protein responsible for regulating RNA stability, splicing, microRNA maturation and the recently reported gene expression [59]. HnRNPA2 can participate in enhancing the tumor potential of cells by directly regulating genes involved in resistance to apoptosis, inflammation, and metastasis [89][90][91][92]. We demonstrated that apigenin inhibits hnRNPA2 dimerization affecting its splicing activity. Notably, MDA-MB-231 cells treated with apigenin show splicing isoforms found in non-tumor cells, suggesting the potential of apigenin to reeducate the aberrant tumor-proteome. It would be interesting to see whether the ability of apigenin to interact with hnRNPA2 increases chemosensitization by overcoming the increased anti-apoptotic protection of tumor cells. Intriguing, hnRNPA2 was found to regulate the splicing of the pyruvate kinase (PKM2/PKM1), suggesting the ability of apigenin to regulate central metabolic hubs responsible for the Warburg's effect [93][94][95][96][97]. Apigenin also directly binds to MUC1 (Mucin 1), a key oncogene participating in tumor growth and metastasis [64][65]. MUC1 is also known to regulate metabolic reprogramming in the MDA-MB-231 cells by altering glutamine dependency of the cells which can be ascribed to the changes in glutamine metabolism [98]. Recent studies also showed that luteolin binds to the transcription factor HNF4α (Hepatocyte Nuclear Factor 4 alpha), repressing fat metabolism [99]. Therefore, understanding these novel mechanisms of action of flavonoids should provide important insights into their prevention and therapeutic potential in breast cancer.

## 3. Dietary Flavonoids and Breast Cancer

Epidemiological studies and systematic analysis suggest that diets rich in flavonoids are inversely associated with BC risk [7][100][101][102][103][104]. The ability of flavonoids to modulate not only cancer cells but also other components of the TME has attracted great interest in the field, providing unique opportunities for the prevention and treatment of BC [5][105]. The health beneficial effects of flavonoids in cancer have been mainly focusing on the cancer cells, seeking to understand the regulation of tumor related genes, signaling pathways, metastasis, and resistance to apoptosis [106][107][108][109][110][111]. However, the breakthrough that flavonoids can modulate the TME provides unforeseen opportunities to halt tumor development, progression and metastasis [112][113][114][115]. Adipocytes, major constituents of BC TME, and its cross talk with cancer cells have strong implications in BC progression, invasion [116][117], induction of aberrant gene expression profiles [118] and therapeutic resistance [119]. Importantly, flavonoids can inhibit adipogenesis, reduce obesity and obesity-related cancer [78][79][120][121]. In addition, adipocytes and macrophages contribute to the tuning of TME making them potential participants of obesity linked cancer and also promising targets for flavonoids [122]. The modulation of T cells by apigenin [61] and dendritic cells (DC) by quercetin [62] can be crucial for overcoming the immunosuppressive condition and inflammation [123][124]. The ability of flavonoids like quercetin and luteolin to target macrophages either by reducing their recruitment into the TME or by reprogramming TAMs from a M2 (tumor promoting) to M1 (tumor suppressive) phenotype has great implications in anti-cancer therapy [73][74][125][126]. Thus, this ability of flavonoids to modulate not only the cancer cells but also other TME accomplices gives them unique opportunities for BC prevention and therapeutic.

### 3.1. Potential Role of Flavonoids in Breast Cancer Therapeutics

Flavonoids have become widely studied in cellular models as a therapeutic agent owing to its low systemic toxicity and broad range of ant-carcinogenic activities. Cancer cells are adaptively resistant to chemotherapeutic drugs, which eventually engender multidrug resistant cells leading to the aggressive tumor growth and metastasis. Sensitization to chemotherapeutic drugs using naturally occurring flavonoids has become an approach of interest aiming to enhance the efficacy of cytotoxic effects, delay the incidence of acquired chemoresistance and halt proliferative pathways [127][128]. Inhibition of transporters like Pgp or MRP by flavonoids like quercetin and luteolin has resulted in an increased bioavailability of cytotoxic drugs, with a potential impact in the quality of life of BC patients [5][129]. Several studies using cellular models have provided strong evidence that flavonoids increase the efficacy of current therapies. Apigenin reduced the expression of MDR1, MRPs and P-gp in MCF-7-doxorubicin resistant cell lines by attenuating STAT3 signaling pathway [63]. Rutin increased the cytotoxicity of cyclophosphamide and methotrexate on MDA-MB-231, MCF-7 and primary human mammary fibroblasts (HMF) in a time dependent manner, by suppressing the expression of P-gp and BCRP, arresting the cells at G2/M and G0/G1 phases and promoting cell apoptosis [64]. Isoflavones also effectively inhibit BCRP [83]. Epigallocatechin gallate with tamoxifen has shown to synergistically enhance the cytotoxic effect against MDA-MB-231 cell lines [65]. Resveratrol chemosensitization to doxorubicin functioned by hindering NFκB andby impeding the expression of Hsp27, an inhibitor of caspase-3, in MCF-7 cell lines [130][131][132]. The resveratrol-doxorubicin combination also showed a 2.5 fold of dose advantage in inhibiting growth, NFκB activity and inducing apoptosis in MDA-MB-231 and MCF-7 cell lines [66]. Apigenin enhanced cisplatin cytotoxicity through a p53 mechanism in MCF-7 cells [67]. Flavopiridol, a semisynthetic flavone and trastuzumab synergistically inhibited the P13k/Akt pathway and induced cell cycle arrest in SK-

BR3 (HER2+) and BT-474 (ER+) cell lines [68]. It was also found to enhance the cytotoxicity induced by sorafenib, a Raf inhibitor, in MDA-MB-231, MDA-MB-468 and SK-BR3 cell lines. Interestingly, this synergy also reduced the primary tumor growth rates and metastatic tumor load in the lungs of MDA-MB-231 mammary fat pad engraftment mouse models, compared to treatment with either drug alone [69]. However, the combinational treatment of flavopiridol with docetaxel and trastuzumab at clinical levels did not report any significant effect. While quercetin or doxorubicin alone failed to cure tumor-bearing mice, a combination regime induced significant depletion of 4T1 BC and led to a long-term, tumor-free survival in mice bearing established breast tumor along with persistent T-cell tumor-specific responses [75]. These findings suggest that the anti-carcinogenic activities of flavonoids might be more effective in combination with other chemotherapeutic agents than when used alone.

Mechanistically some flavonoids have been shown to increase the expression of receptors of therapeutic drugs. Flavones like chrysin [133], luteolin [134] and apigenin [135] have increased the expression of TRAIL receptor DR5 and thereby contributing to TRAIL induced and chemotherapeutic induced cytotoxicity in multiple cancer cell lines by inhibiting the NFκB pathway and activation of caspase-3, -8, -9 and -10. Thus, flavonoid and TRAIL combination treatments can be a promising therapy against malignant breast tumors. As potent apoptosis inducers, flavonoids are known to possess cytotoxicity against cancer cells. Apigenin can induce apoptosis through caspase activation, PARP cleavage and pro- and anti-apoptotic markers Bax/Bcl-2 ratio [70]. In BT-474 and MDA-MB-231 xenograft mice models, apigenin attenuated growth through the induction of apoptosis and inhibition of proteasome activity and VEGF [76][77]. Interestingly, wogonin, chrysin and apigenin were shown to induce TRAIL mediated apoptosis in MDA-MB-231 by downregulating cellular FLICE-like inhibitory protein (c-FLIP) expression and enhancing the expression of TRAIL DR5 [71]. We have earlier reported that apigenin, through its direct interaction with hnRNPA2, can reduce the levels of splice isoform of c-FLIP (c-FLIP$_S$) and caspase-9 (caspase-9b) in MDA-MB-231, two key RNA isoforms that when translated play a role in inhibiting apoptosis in cancer cells [59]. These findings together uphold the therapeutic effect of flavones such as apigenin in breast cancer cells, emphasizing the need for more studies in xenograft and preclinical models. Current research is also investigating the tuning of TME cells with the aid of flavonoids in order to enhance the effect of the chemotherapeutic drugs. Cellular studies show that genistein enhances the natural killer cell mediated cytotoxicity in MCF-7 cell lines [136][137]. Hence, there is an increasing need to identify chemosensitizers targeting preferentially to the tumor site that can provide low systemic toxicity and enhanced therapeutic drug efficacy. This clearly suggests the potential benefit of flavonoids as a chemosensitizer and an immunomodulator and hence emphasizes the need for combinational therapy as an approach to treat BC.

### 3.2. Potential Role of Flavonoids in Breast Cancer Prevention

Several epidemiological studies have shown that flavonoid rich diets are associated with the reduction of cancer risk in humans [138]. Mediterranean and Asian diets, which are highly rich in flavonoids, are often linked to a reduced risk of BC [139][140][141]. Increased consumption of isoflavones decreased the risk of estrogen-related cancers [142][143]. In a meta-analysis of 12 prospective cohort or case-control studies, the risk of BC was shown to be significantly decreased in women with a high intake of flavonols and flavones among post-menopausal women [102]. The Shanghai Women's Health Study showed higher levels of urinary epicatechins relating to a lesser incidence of breast cancer [144]. Similarly, several case control studies have reported that an increased intake of flavones can reduce the BC risk in women [100][101][104].

Obesity is reaching epidemic levels across the world [145]. Approximately 35% of the adult US population is overweight [146]. Obesity is often associated with a higher risk of developing BC and worse disease outcomes for women of all ages, irrespective of menopausal status [147]. In the Breast Cancer Prevention P-1 trial and World Health Initiative trial I, two among the many clinical trials conducted on obesity-BC relation, found that obesity was strongly associated with higher premenopausal [148] and postmenopausal BC risk [149], respectively. The Million Women Study, which included 45,037 breast cancer women between the ages of 50–64 years, identified a 30% higher risk of developing postmenopausal breast cancer with obesity in UK women [150]. However, studies have shown that the risk for TNBC is higher among premenopausal women. The Cancer and Steroid Hormone, a population-based case-control study involving 3432 BC patients, reported a strong positive association between body mass index (BMI) and premenopausal TNBC risk [151]. Similarly, two meta-analyses of 1358 [152] and 620 [153] TNBC patients showed an 80% and 43% higher risk of developing TNBC in obese premenopausal women, respectively. Adipose tissues secrete cytokines and mediators which participate in creating an environment that favors cancer invasion and metastasis and are highly amplified in obese individuals [154]. Increased inflammatory condition, a characteristic of obesity, has also been largely associated to increased incidences and poor clinical outcomes [155][156][157]. Obese individuals display dysregulated genes expression, harboring TME inflammatory conditions that increase macrophage infiltration and adipokine imbalance in breast tissues [157][158][159]. Interestingly, a recent retrospective study showed a relation between obesity and the development of metastasis in BC patients and indicated that non-obese patients showed a better response to first-line metastatic chemotherapy treatment

when compared to obese patients [160]. Investigations on flavonoids as potent agents against obesity and obesity-linked BC are gaining great interest. A study involving 9551 adults who participated in the National Health and Nutrition Examination Survey 2005–2008 reported that flavonoid consumption was inversely related to obesity in multivariate models of both men and women with significant reduction in BMI and C-reactive protein, a marker for inflammation, in US adults. Flavonoids from wheat (*Triticum aestivum*) sprout showed an inhibitory effect on adipogenesis through the downregulation of genes associated with lipid metabolism and adipogenic transcription factors [161]. Adipocytes are known to be potent modulators and recruiters of TAMs, thereby actively contributing to tumor growth. Luteolin strongly inhibited the interaction between 3T3-L1 adipocytes and RAW246 macrophages, thereby suppressing the production of pro-inflammatory mediators like TNF-α [72]. In animal models, flavonoid-enriched extract from *Hippophaerhamnoides L.* seed induced anti-obesity activities in high fat diet (HFD) C57BL/6 mice and recruited macrophage infiltration into the adipose tissues [79]. Naringenin not only reduced adipose mass and inflammation but had a moderate effect on the inhibition of tumor growth in C57BL/6 mice injected with E0771 mammary carcinoma cell line [88]. Resveratrol was reported to inhibit obesity-associated inflammation and claudin-low BC growth in diet induced obese C57BL/6 mice by inhibiting adipocyte hypertrophy and associated adipose tissue dysregulation [80]. Interestingly, two recent independent studies provided preclinical evidence using MMTV-PyMT murine models of BC that mammary adipose tissue inflammation induced by diet enhanced the recruitment of macrophages, increased tumor vascular density [162] and hormone production in pre- and postmenopausal hormone receptor positive BRCA [163], suggesting a role for obesity in creating a microenvironment favorable for the progression of breast cancer. However, there is a scarcity of data on the effect of flavonoids on HFD induced mammary tumorigenesis in preclinical PyMT mouse models, which can be highly corroborative for clinical studies targeting cancer prevention.

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