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Opportunities, obstacles and current challenges of flavonoids for luminal and triple-negative breast cancer therapy

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ABSTRACT

Flavonoids are a large group of polyphenols with numerous biological effects on cancer cells. They have been shown to affect proliferation *via* cell cycle arrest, apoptosis and necrosis and to exert anti-oxidant, anti-inflammatory and anti-mutagenic actions. Anti-cancer effects of flavonoids, mostly in preclinical evaluations, should be translated into clinical cancer treatment research, where evidence is still scarce. Although therapies targeting primary breast tumors have markedly improved, those targeting elusive micro-metastases are less effective. In this scenario, the present review discusses the anti-tumor effects of different simple natural and synthetic flavonoids on luminal and triple-negative breast cancer, highlighting biological effects such as apoptosis, epithelial-mesenchymal transition reversion, cell migration and invasion inhibition, metalloprotease inactivation/down-regulation and anti-angiogenesis, as well as compiling *in vivo* treatments in experimental tumor models and some specific clinical trials. In addition, this review discusses the mechanisms underlying flavonoid anti-tumor effects. Moreover, although flavonoids may be regarded as a spectrum of promising polyphenols with multifaceted anti-tumor effects, mainly applicable to metastatic breast cancer management, some major challenges and concerns about potential flavonoid therapy in luminal and triple-negative breast cancer are also discussed.

1. Introduction

Flavonoids (from the Latin word *flavus*, meaning yellow, due to their color in nature) are a large group of polyphenols with low molecular weight present in almost all fruits and vegetables [1]. Natural flavonoids constitute a family of around 15,000 compounds that contribute to the colorful pigments of fruits, herbs, vegetables and medicinal plants, attracting pollinators and helping seed and spore germination, growth and development. Flavonoids protect plants from different biotic and abiotic stresses and act as unique UV filters, signal molecules, detoxifying and antimicrobial agents [2].

In human diet, the physicochemical properties of flavonoids influence their metabolic fate, *i.e.,* their digestion, absorption and biotransformation. In fact, these compounds generally possess low bioavailability when orally administered in humans, mainly due to their low solubility and hepatic metabolism by phase-I and II enzymes [3]. Many natural and synthetic flavonoids are substrates for glucuronidation, *O*-methylation and sulfation in small-intestine epithelial cells, modifications that decrease their bioactivity [4]. In particular, human gut microbial enzymes transform flavonoids through deglycosylation, ring fission, dehydroxylation, demethylation into metabolites that can then be absorbed or excreted [5]. Importantly, certain substituents in synthetic flavonoid (*i.e.* glycosylation) can greatly improve their pharmacokinetics profile [6].

In cancer cells, flavonoids produce numerous biological effects as they impact growth *via* cell cycle arrest, apoptosis and necrosis and exhibit anti-oxidant, anti-inflammatory, anti-mutagenic and antineoplastic properties. Of note, flavonoids affect cell proliferation through a wide range of mechanisms and some of them might interact with diverse cellular molecules such as enzymes, growth factors, metalloproteases, transcription factors and nucleic acids, among others [7,8]. In this context, the present work reviews the anti-tumor effects of different simple and most common flavonoids on luminal cancer and triple-negative breast cancer (TNBC). Special emphasis is placed on major antineoplastic effects such as apoptosis, the inhibition of cell

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migration and invasion, metalloprotease inactivation/down-regulation, the reversion of epithelial-mesenchymal transition (EMT) and anti-angiogenesis, as well as on *in vivo* treatments in preclinical tumor models. We also analyze several concerns for flavonoid therapy in luminal and triple-negative breast cancer.

2. Chemical classification of flavonoids

A class of polyphenolic secondary metabolites found in plants, flavonoids, have a general structure of a 15-carbon skeleton which consists of two phenyl rings (A and B) and a heterocyclic ring (C, containing the oxygen atom) and can be abbreviated as C6–C3–C6 [9,10]. According to the IUPAC nomenclature [11], they can be classified into flavonoids, isoflavonoids and neoflavonoids (Fig. 1), derived from 2-phenylchromen-4-one (flavone), 3-phenylchromen-4-one (isoflavone) and 4-phenylchromen-2-one (phenylcoumarin), respectively (Fig. 2). Derivatives include reduction of the C2–C3 carbon-carbon double bond (flavanones), hydroxylation at position 3 in ring C (flavonols), reduction of the keto group (flavans), opening of ring C (chalcones), oxidation of the C2–O1 carbon-oxygen bond (anthocyanidins) and a 5-membered ring C (aurones) (Fig. 2). The chemical diversity of flavonoids is particularly obtained from glycosylation, methoxylation, prenylation and hydroxylation, among others, which usually occur in specific positions in the different classes. *O*-glycosides are the most abundant form of flavonoid glycosides, although *C*-glycosides can also be found. Glycosylation enhances solubility, distribution and metabolism by facilitating transport through the membrane, while methylation increases flavonoid entry into cells [12]. Table 1 summarizes the flavonoids with anti-tumor actions discussed in this review according to their structural classification.

3. Breast cancer

Breast cancer is one of the most common types of cancer and shows increasing incidence rates. According to GLOBOCAN 2020, which estimated cancer incidence and mortality from the International Agency for Research on Cancer, 2,261,419 new cases were reported worldwide in 2020 and 684,996 female patients died as a result of mammary tumors [13]. Breast cancer gene expression profiles reveal four major breast cancer molecular subtypes: luminal A, luminal B, basal-like (including TNBC) and human epidermal growth factor receptor 2 (HER2)-enriched [14–17]. Although bone, lung, liver and brain are generally accepted as primary target sites of breast cancer metastasis, early prognostic/predictive methods to determine organ susceptibility are still scarce, and the molecular mechanisms of metastatic heterogeneity remain to be fully elucidated. Moreover, for patients with early-stage breast cancer, the estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki-67 antigen (Ki67) expression profiles of recurrent/metastatic tumors do not always match that of the primary tumor. Therefore, adjusting treatment according to receptor expression in recurrent/metastatic lesions might enable patients to remain progression-free [18].

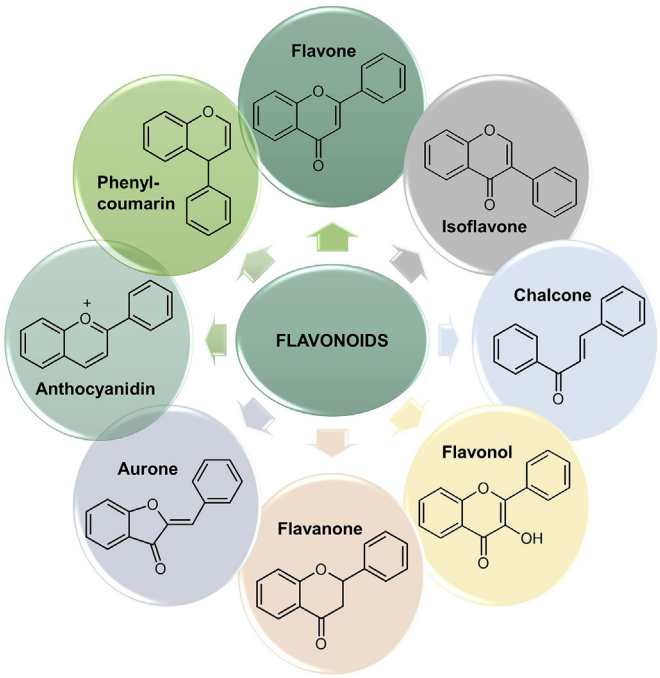


Fig. 2. Different structures of the major flavonoid classes reported in the literature. Derivatives of basic compounds from Fig. 1 include reduction of the 2(3) carbon-carbon double bond (flavanones), hydroxylation at position 3 in ring C (flavonols), reduction of the keto group (flavans), opening of the C ring (chalcones) and oxidation of the 2(1) carbon-oxygen bond (anthocyanidins). Some other flavonoid derivatives are aurones and chalcones.

Genomic and pathologic approaches, imaging analysis and animal modeling have yielded new insights into more effective therapeutics. However, current treatments for metastatic breast cancer have been mostly ineffective, with a large proportion of patients developing drug resistance [18,19]. Therefore, targeted therapy requires the development of new compounds. In this scenario, the following sections summarize the anti-tumor effects of certain natural and synthetic simple flavonoids on luminal cancer and TNBC, with a view to unveiling flavonoid participation in apoptosis, the inhibition of cell migration and invasion, the reversion of EMT as well as in the inhibition of angiogenesis. Finally, current challenges and major concerns on flavonoid application in breast cancer therapy are also discussed.

3.1. Flavonoids in luminal breast cancer

Luminal breast cancer comprises ERα-positive tumors and constitutes the largest breast cancer subgroup. Patients are submitted to endocrine

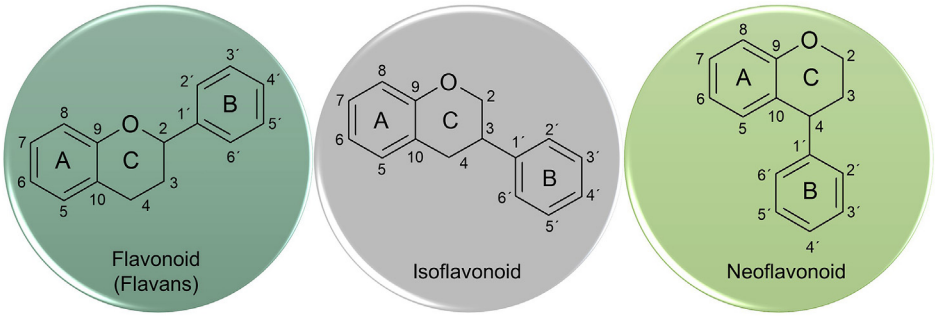
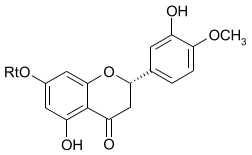
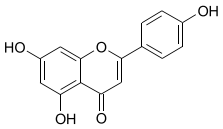
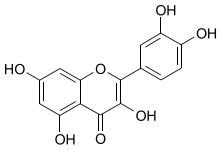
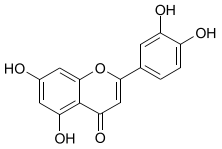
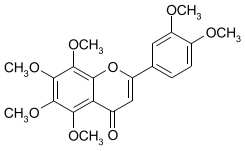
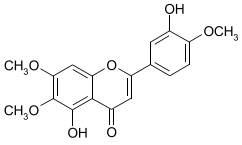
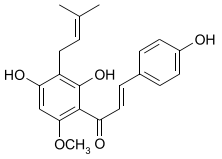
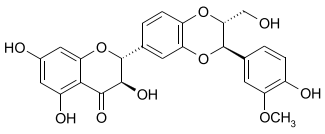
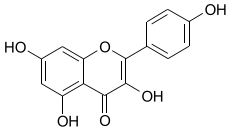
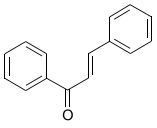
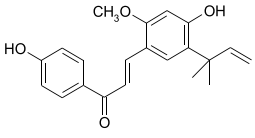


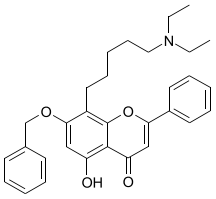
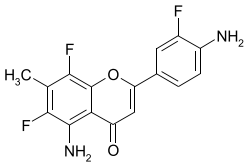
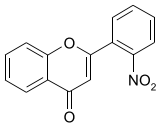
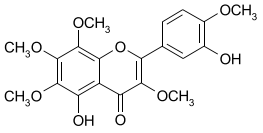
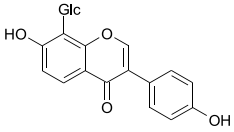
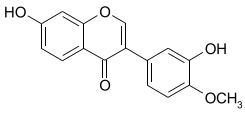
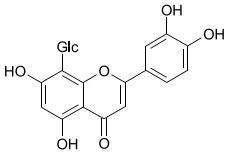
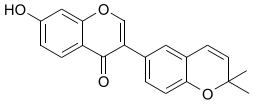
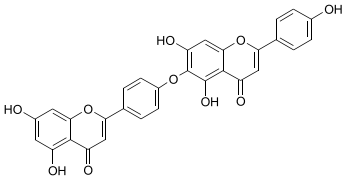
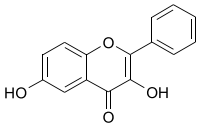
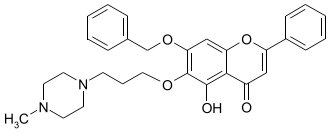
Fig. 1. Basic classification of flavonoid skeletons and carbon numbering pattern. Flavonoid chemical structures have a general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and a heterocyclic ring (C, containing the oxygen atom). This carbon structure can be abbreviated as C6–C3–C6. According to IUPAC nomenclature, they can be classified into flavonoids, isoflavonoids and neoflavonoids.

Table 1
Molecular structures of the flavonoids described in this review.

Compound number#	Compound name	Structure	Flavonoid type	Ref.
1	Hesperidin		Flavanone glycoside	[26]
2	Apigenin		Flavone	[124]
3	Quercetin		Flavonol	[97]
4	Luteolin		Flavone	[100]
5	Nobiletin		Flavone	[33]
6	Eupatorin		Flavone	[37]
7	Xanthohumol		Prenylated chalcone	[38]
8	Silibinin		Flavonolignan (part flavonoid and part phenylpropan)	[42]
9	Kaempferol		Flavonol	[43]
10	Chalcone		Chalcone	[48]
11	Licochalcone A		Chalcone	[48]
12	LW-214*		Flavone	[49]

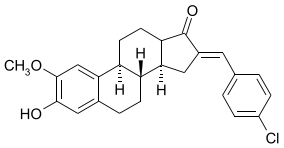
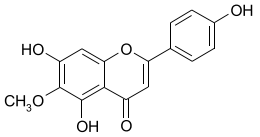
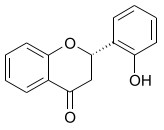
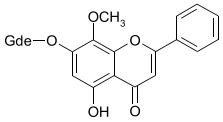
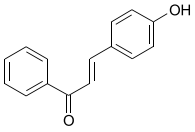
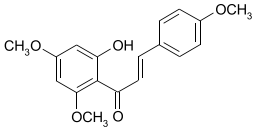
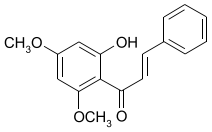
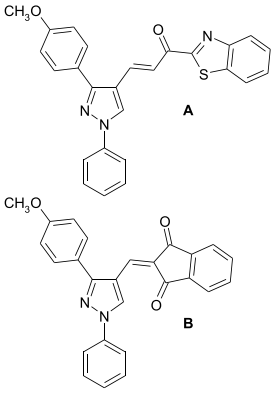
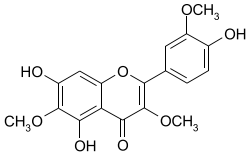
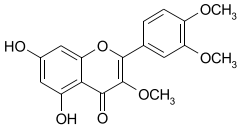
(*continued on next page*)

Table 1 (*continued*)

Compound number#	Compound name	Structure	Flavonoid type	Ref.
				
13	NSC 686288*		Flavone	[53]
14	2′-Nitroflavone		Flavone	[56]
15	Pentamethoxylated-flavone*		Flavone	[59]
16	Puerarin		Isoflavone C-glycoside	[60]
17	Calycosin		Isoflavone	[62]
18	Orientin		Flavone C-glycoside	[63]
19	Corylin		Isoflavone	[64]
20	Hinokiflavone		Biflavone	[65]
21	3,6-Dihydroxy-flavone		Flavonol	[70]
22	LFG-500*		Flavone	[74]
23	Compound 11e*		Chalcone	[75]

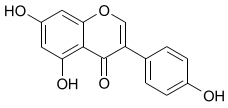
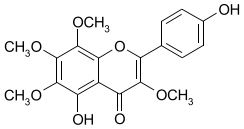
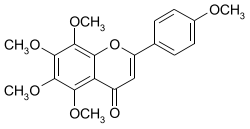
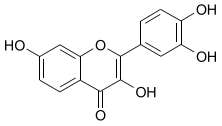
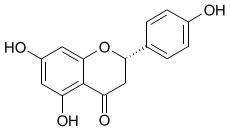
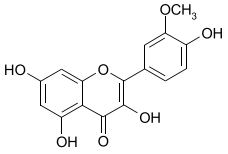
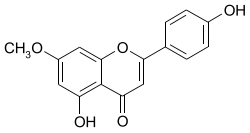
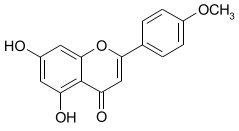
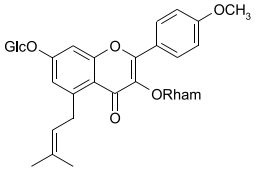
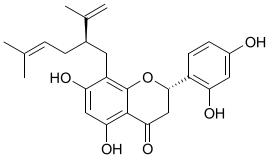
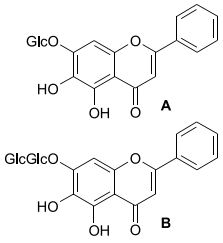
(*continued on next page*)

Table 1 (*continued*)

Compound number#	Compound name	Structure	Flavonoid type	Ref.
				
24	Hispidulin		Flavone	[78]
25	2′-Hydroxy-flavanone		Flavanone	[82]
26	Wogonoside		Flavone glycoside	[99]
27	4-Hydroxy-chalcone		Chalcone	[101]
28	Flavokawain A		Chalcone	[102]
29	Flavokawain B		Chalcone	[103]
30 A,B	Chalcone 3 (**30A**) and 5 (**30B**)*		Chalcone	[106]
31	Jaceidin		Flavonol	[107]
32	Compound 3*		Flavonol	[107]
33	Genistein		Isoflavone	[109]

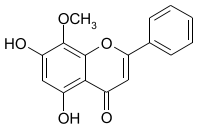
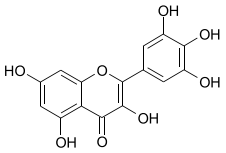
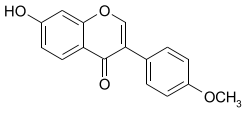
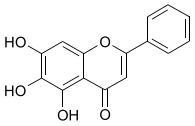
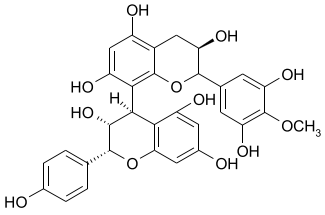
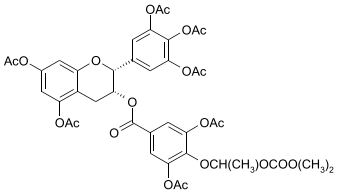
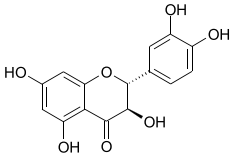
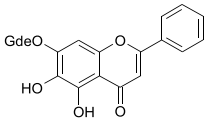
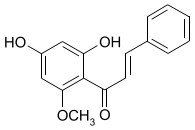
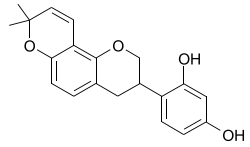
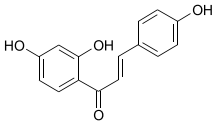
(*continued on next page*)

Table 1 (*continued*)

Compound number#	Compound name	Structure	Flavonoid type	Ref.
				
34	Calycopterin		Flavonol	[110]
35	Tangeretin		Flavone	[111]
36	Fisetin		Flavonol	[113]
37	Naringenin		Flavanone	[114]
38	Isorhamnetin		Flavone	[115]
39	Genkwanin		Flavone	[115]
40	Acacetin		Flavone	[115]
41	Icariin		Prenylated flavonol glycoside	[116]
42	Sophoraflavanone G		Prenylated flavanone	[117]
43	Oroxin		Flavone glycoside	[120]
44	Wogonin		Flavone	[121]

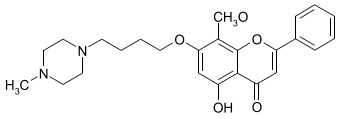
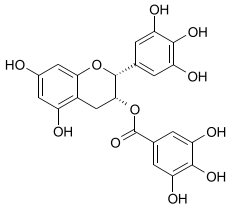
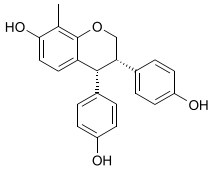
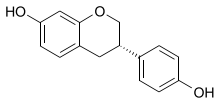
(*continued on next page*)

Table 1 (*continued*)

Compound number#	Compound name	Structure	Flavonoid type	Ref.
				
45	Myricetin		Flavonol	[127]
46	Formononetin		Isoflavone	[129]
47	Baicalein		Flavone	[131]
48	Proanthocyanidin		Anthocyanidin	[132]
49	EGCG derivative*		Flavanol	[133]
50	Taxifolin		Flavanol	[135]
51	Baicalin		Flavone	[136]
52	Cardamonin		Chalcone	[140]
53	Glabridin		Isoflavane	[143]
54	Isoliquiritegenin		Chalcone	[145]
55	LYG-202*		Flavone	[148]

(*continued on next page*)

Table 1 (*continued*)

Compound number#	Compound name	Structure	Flavonoid type	Ref.
				
56	Epigallocatechin 3 galate		Flavanol	[159]
57	ME-344		Isoflavane/Neoflavane	[167]
58	S-Equol		Isoflavane	[166]

Sugar moieties: Glucose (Glc); Rutinose: *O*-α-L Rhamnosyl-(1 → 6)-glucose (Rt); Glucuronide (Gde); Rhamnose (Rham). * Name reported in the literature. # In this review, synthetic flavonoids have been named with the compound number assigned in this Table 1.

ER-directed therapy which prolongs survival and shows a highly favorable prognosis [20,21]. Tamoxifen (TAM) is a non-steroidal compound that binds competitively to ERα and is used after surgery as first-line endocrine therapy against luminal mammary tumors in pre-menopausal women. However, 40% of patients who initially respond effectively to TAM administration develop secondary resistance during its standard 5-year treatment [22]. Some natural and synthetic simple flavonoid effects on luminal tumors and the potential underlying mechanisms are described in the following sections and summarized in Table 2. Half-maximal inhibitory concentration (IC_{50}) values of flavonoids and some common antitumor agents are included in Table 2 to compare their relative antitumor potency mainly in MCF-7 cells.

3.1.1. Effects of flavonoids on cell cycle arrest, inhibition of proliferation and apoptosis induction

Flavonoids of propolis, such as hesperidin (**1**), apigenin (**2**) and quercetin (**3**), dose-dependently produced cell cycle arrest in ER-positive PR-positive human luminal A breast adenocarcinoma MCF-7 cells. For example, 50 μM hesperidin (**1**) increased the number of cells in the G0/G1 phase to 48%, while 100 μM reduced cells in the S phase to 36% and increased those in G0/G1 to 54%. Apigenin (**2**) induced the G0/G1 phase in 65% of cells at both 50 μM and 100 μM. Quercetin (**3**) increased the number of cells in the G2/M phase to 15% and 25% and those in the S phase to 31% and 39% at 50 μM and 100 μM, respectively [22,23]. Quercetin (**3**) has also been proposed to reverse TAM resistance. TAM-resistant MCF-7 (MCF-7Ca/TAM-R) cells showed no inhibition of proliferation after treatment with low TAM concentrations; however, the simultaneous or sequential administration of quercetin (**3**) and TAM significantly reduced survival rates, as observed in 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assays. Most importantly, quercetin (**3**) boosted MCF-7Ca/TAM-R cell apoptosis, as measured through propidium iodide (PI) staining in flow cytometry analyses; an increase in quercetin (**3**) dosage to 50 μM also increased apoptosis, with no differences between simultaneous and sequential co-administration with TAM. Moreover, results showed gradual down-regulation in HER2 expression and up-regulation in ERα, which further suggests that quercetin (**3**) reversed TAM resistance in MCF-7Ca/TAM-R cells [24]. In MCF-7 cells, hesperidin (**1**) produced cytotoxicity, cell shrinkage, chromatin condensation and apoptotic bodies, associated with late apoptosis and inhibited colony formation [25]. Furthermore, *in vivo*, lipopolysaccharide (LPS)-challenged hesperidin-treated mice presented an improved anti-inflammatory reaction resulting in lower levels of interleukin-33 (IL-33) and tumor necrosis factor α (TNFα) and higher glutathione levels and catalase activity, which hints at the free radical scavenging potential of this flavonoid [25]. In addition, hesperidin-treated MCF-7 cells showed an increase in caspase-3, -9 and B-cell lymphoma 2 (BCL-2)-associated X (BAX) protein expression, along with a decrease in BCL-2 protein levels. Finally, hesperidin (**1**) also increased the expression levels of micro-RNA (miR)-16 and −34a (which are known to promote apoptosis) and down-regulated miR-21 [26].

Luteolin (**4**) treatment produced large accumulation of MCF-7 cells in the sub-G1 phase, with an increase in the expression of caspase-9, -8, miR-16 and -34a [26,27]. Also in MCF-7 cells, luteolin (**4**) activated caspase-8 and subsequently induced caspase-3 activity in the extrinsic apoptotic pathway; in contrast, luteolin (**4**) increased BAX and reduced BCL-2 expression in the intrinsic pathway, affecting mitochondrial membrane integrity and contributing to increased caspase-3 activity *via* caspase-9 activation [28]. Luteolin-7-*O*-glucoside from *Cuminum cyminum* demonstrated potent anti-cancer activity against MCF-7 cells, being the sugar position proposed to improve flavonoid cellular uptake and inhibitory activity [29]. In addition, luteolin-mediated regulation of p21, cyclin-dependent kinases (CDKs) and cyclins potentiated cell cycle arrest in MCF-7 cells but showed a biphasic effect, inducing an increase in p21 (a major target of the tumor suppressor p53) at low doses and a decrease at higher doses [30,31]. Luteolin (**4**) also reduced insulin-like growth factor 1 (IGF-1)-dependent receptor (IGF-1R) and AKT phosphorylation without affecting ERK1/2 phosphorylation. Lower ERα expression indicates direct involvement of ERα in cell growth inhibition by luteolin (**4**); indeed, ERα knockdown in MCF-7 cells reduced IGF-1-induced cell growth inhibition by luteolin (**4**), revealing ERα as a possible target of this flavonoid [32].

Nobiletin (**5**) produced anti-proliferative effects in MCF-7 cells [33,34], rendering a cell cycle blockade in G1 and a reduction in cell

Table 2
Effects of some flavonoids on luminal breast cancer.

Flavonoid	CELL CYCLE, PROLIFERATION, APOPTOSIS				
	Accumulation/increase	**Down-regulation/inhibition**	**Human cell lines IC_{50} (μM)**	***In vivo*[a]**	**Ref.**
Hesperidin (**1**); Apigenin (**2**); Quercetin (**3**) (propolis)	G0/G1 phase		MCF-7 *(9)***; *(25)***; *(95)***	nd	[23]
Quercetin (**3**) + TAM	ERα	HER2	MCF-7Ca/TAM-R *(78)***	nd	[24]
Hesperidin (**1**)	G0/G1 phase; caspase-3 and -9 expression; BAX	BCL-2	MCF-7 *(nd)*	nd	[26]
Luteolin (**4**)	sub G1 phase; caspase-8 and -9 expression; BAX	BCL-2; pIGF-1R; pAKT; ERα	MCF-7 *(nd)*	nd	[26, 31]
Nobiletin (**5**)	CYP1 enzyme activity; CYP1A1 protein; CYP1B1 mRNA	G1 block	MCF-7 *(44)*****	nd	[33]
Eupatorin (**6**)	G2/M phase; BAX; caspase-9 and -8 activity; RAF-1	BCL2L11, VEGFA; HIF1A; CHK1 and 2; AKT	MCF-7 *(5)***	nd	[37]
Xanthohumol (**7**)	G1 arrest	pAKT (S473), pMAPK (T202/Y204) and pERα (S104/S106, S118, S167, S305, Y537)	MCF-7 *(7)*** KPL-3C	*Nude*/KPL-3C	[38]
Silibinin (**8**)	BAX; release of mitochondrial cytochrome *c*; nuclear translocation of AIF; ERβ; autophagy; caspase-8 activity	BCL-2; ERα	MCF7 *(200)*** T47D	nd	[39, 42]
Kaempferol (**9**)	cleaved PARP; BAX	BCL-2; pIRS-1, pAKT, pMEK1/2 and pERK1/2	MCF-7 *(50)*****	*Nude*/MCF-7	[43, 47]
Chalcone (**10**); Licochalcone A (**11**)	plasma membrane damage; BAX; cleaved PARP; CIDEA	S and G2/M phases; BCL-2; cyclin-D1	MCF-7 *(42)***; *(23)***	nd	[48]
Compound **12**	BAX; cleaved PARP; cleaved caspase-9; ROS; release of mitochondrial cytochrome *c*; nuclear translocation of AIF; pJNK; pASK1	BCL-2; TRX-1	MCF-7 *(5)***	*Nude*/MCF-7	[49]
Compound **13**	cleaved PARP; cleaved caspase-9; ROS	AhR signaling; CYP1A1; CYP1B1	MCF-7 *(0.00013)***	nd	[53]
2′-Nitroflavone (**14**)		cytotoxicity	MCF-7 *(6)****	nd	[56]
Flavonoid	**CELL MIGRATION & INVASION**		**Human cell lines IC_{50} (μM)**	***In vivo*[a]**	**Ref.**
	Up-regulation /increase	**Down-regulation /reduction**			
Pentamethoxylated-flavone (**15**)		wound-healing; NF-κB p65	MCF-7 *(17.3)***	nd	[59]
Puerarin (**16**)		transwell migration; Matrigel™ invasion assay; MMP-9; MMP-2; CCR7; CXCR4; VCAM-1; ICAM-1; TNFα; IL-6; pNF-κB p65; pIκBα; pERK1/2	MCF-7 + LPS *(80)**	nd	[60]
Calycosin (**17**)		wound-healing; invasion assay; FOXP3; MMP-9; VEGF	MCF-7 *(>150)*** T47D	nd	[62]
Orientin (**18**)		wound-healing; matrigel invasion assay; MMP-9; IL-8; PCKα membrane translocation; pERK; c-JUN, c-FOS, STAT3 nuclear translocation	MCF-7 + TPA *(not cytotoxic)*	nd	[63]
Corylin (**19**)	miR-34c	wound-healing; Matrigel™ invasion assay; LINC00963 mRNA	MCF-7 *(11)***	nd	[64]
Hinokiflavone (**20**)		MMP-9; cytotoxicity	MCF-7 *(43)***	nd	[65]
	DOCKING Target: MMP-9				
Flavonoid	**EPITHELIAL-MESENCHYMAL TRANSITION**		**Human cell lines IC_{50} (μM)**	***In vivo*[a]**	**Ref.**
	Up-regulation	**Down-regulation/reduction**			
3,6-Dihydroxy flavone (**21**)	E-cadherin	SNAIL; TWIST; SLUG; N-cadherin; NOTCH1; NICD	MCF-7 *(nd)*	nd	[70]
Compound **22**	ZO-1; E-cadherin; pYAP; pMST1/2; pLATS1/2	N-cadherin; vimentin; SLUG; SNAIL; YAP; ILK	MCF-7 *(nd)*	MMTV-PyMT transgenic mice	[74]
Compound **23**	ZO-1; E-cadherin	N-cadherin; vimentin	MCF-7 *(70)****	*Nude*/MCF-7	[75]
Hispidulin (**24**)	E-cadherin	occludin; pSMAD2/3	MCF-7 *(25)**	nd	[78]
Calycosin (**17**)	E-cadherin	N-cadherin; vimentin; CD147, MMP-2; MMP-9; BATF	MCF-7 *(400)*** T47D	*Nude*/T47D	[80]
2′-Hydroxy flavanone (**25**)	E-cadherin	vimentin; RLIP76; ERα	MCF-7 *(24)***	*Nude*/MCF-7	[81, 82]
	DOCKING Targets: ERα; RLIP76; HER2				[83]
Kaempferol (**9**) + E2	E-cadherin	N-cadherin; SNAIL; SLUG; cathepsin D; MMP-9; MMP-2	MCF-7 *(nd)*	nd	[88]
	DOCKING Target: ERα				[87]
Flavonoid	**ANGIOGENESIS**		**Human cell lines IC_{50} (μM)**	***In vivo*[a]**	**Ref.**
	Promotion	**Inhibition/reduction**			
Quercetin (**3**)		vWF; tumor microvessel density; VEGF; VEGFR2; calcineurin activity; NFAT	MCF-7 (*nd*)	*Nude*/MCF-7	[97]

(*continued on next page*)

Table 2 (*continued*)

DOCKING Target: calcineurin				[95]
Wogonoside (**26**)	VEGF; VEGF promoter activity; EC migration; EC invasion; tubulogenesis	MCF-7 *(>100)*** HUVEC	*Nude*/MCF-7	[99]
Luteolin (**4**)	VEGF secretion/mRNA; tumor microvessel density; tumor VEGF	T47D *(20)***	*Nude*/T47D	[100]
Compound **30A**; **30B**	VEGF mRNA	MCF-7 *(19.8)***; *(9.6)***	nd	[106]
Jaceidin (**31**); Compound **32**	serum VEGF	MCF-7 *(9)***; *(11)***	Swiss albino /Ehrlich Ascites Carcinoma cells	[107]
DOCKING Target: VEGFR [comparison with quercetin (3) and genistein (33)]				

*Half-maximal inhibitory concentration (IC_{50}) after 24 h-treatment.
**IC_{50} after 48 h-treatment.
***IC_{50} after 72 h-treatment.
****IC_{50} after 96 h-treatment. For comparison, IC_{50} (μM) for MCF-7 cells after 48 h-treatment with 4-hydroxy-tamoxifen, fulvestrant, anastrozole, doxorubicin, paclitaxel, taxol and cisplatin are: 21.41 [168], 0.0008 [169], 4.09 [170], 0.69 [171], 0.019 [172], 0.014 [172] and 11.9 [173], respectively.
[a] Mice/cell line inoculated. nd: not determined. EC: endothelial cell.

percentages in the S and G2/M phases [33]. In addition, nobiletin (**5**) induced cytochrome P450 family 1 (CYP1) enzyme activity, CYP1A1 protein and CYP1B1 mRNA levels in MCF-7 cells, while mRNA levels of aryl hydrocarbon receptor (AhR, a transcription factor involved in CYP expression [35,36]) were barely detectable. MCF-7 cell incubation with nobiletin (**5**) mainly produced a metabolite resulting from *O*-demethylation in either ring A or B of the flavone moiety. In fact, CYP1A1 produced a high rate of nobiletin (**5**) metabolism, as demonstrated through recombinant CYP microsomal enzymes. Therefore, nobiletin (**5**) seems to induce its own metabolism, enhancing its cytostatic effect on MCF-7 cells *via* CYP1A1 and CYP1B1 up-regulation [33].

Eupatorin (**6**) also inhibited MCF-7 cell proliferation, mostly producing cell cycle arrest in the G2/M phase at 72 h, with over 50% of cells suffering late apoptosis. Upon eupatorin (**6**) treatment, *BAX* gene was up-regulated, BCL-2 like 11 (*BCL2L11*), vascular endothelial growth factor (VEGF) A (*VEGFA*) and hypoxia-inducible factor 1 subunit alpha (*HIF1A*) genes were down-regulated, and BCL-2 antagonist/killer 1 (*BAK1*) gene expression was unaltered. Caspase-9 and -8 activities were also increased after treatment. Eupatorin (**6**) also suppressed cell cycle checkpoint kinase-1 (CHK1) and −2 (CHK2) protein expression and markedly reduced AKT protein levels, affecting the phosphorylated AKT (pAKT) pathway [37]. In turn, xanthohumol (**7**) inhibited the proliferation of ERα-positive breast cancer cells. The brefeldin A-inhibited guanine nucleotide-exchange protein 3 (BIG3)-prohibitin 2 (PHB2) complex plays a pivotal role in 17β−estradiol (E2) signaling; of note, xanthohumol (**7**) directly bound to PHB2 targeting the BIG3-PHB2 complex in MCF-7 and human ERα-positive KPL-3C cells, which highly express both BIG3 and PHB2 [38]. In the presence of E2, treatment with xanthohumol (**7**) decreased cytoplasmic PHB2, thereby increasing nuclear PHB2 levels. Furthermore, co-immunoprecipitation with an anti-ERα antibody showed that PHB2 released from BIG3 by xanthohumol (**7**) interacted with cytoplasmic and nuclear ERα. Xanthohumol (**7**) showed inhibitory action on ERα transcriptional activity, as demonstrated through luciferase assays in MCF-7 and KPL-3C cells, and blocked E2-induced AKT, mitogen-activated protein kinase (MAPK) and ERα phosphorylation. In addition, xanthohumol (**7**) reduced E2-dependent cell growth, inducing cell cycle arrest in G1, and suppressed E2-induced expression of ERα target genes such as trefoil factor 1 (*TFF1*) and cyclin D1 (*CCND1*). *In vivo*, xanthohumol (**7**) anti-tumor efficacy was demonstrated in a xenograft model of KPL-3C cells in which the flavonoid significantly inhibited tumor growth induced by daily E2 treatment. Moreover, co-immunoprecipitation in tumor samples revealed that xanthohumol (**7**) effectively inhibited endogenous BIG3-PHB2 complex formation [38].

Silibinin (**8**) promoted apoptosis and nuclear translocation of apoptosis-inducing factor (AIF) in MCF-7 cells. Regarding mitochondrial proteins, increased BAX, decreased BCL-2 and the release of cytochrome *c* to extra-mitochondrial compartments were detected after treatment, in keeping with a decline in mitochondrial membrane potential. Interestingly, AIF small interfering RNA (siRNA) partially attenuated silibinin-induced apoptosis, BAX increase, BCL-2 reduction and cytochrome *c* release [39]. Silibinin (**8**) activation of caspases induced apoptosis in MCF-7 cells by down-regulating ERα and up-regulating ERβ protein expression [40,41]. Both mitochondrial and extra-mitochondrial ERα was reduced in silibinin-treated cells, while ERβ was increased both in mitochondrial and extra-mitochondrial protein lysates. Moreover, the nuclear translocation of AIF induced by silibinin (**8**) was attenuated by ERα agonists and ERβ antagonists. Silibinin (**8**) also induced autophagy (finally leading to cell apoptosis) negatively controlled by ERα signaling but not influenced by ERβ signaling [39]. In ER-positive PR-positive T47D human luminal A breast adenocarcinoma cells, the apoptotic response to silibinin (**8**) was more severe than in MCF-7 cells, including earlier apoptotic changes and caspase-3 activation [42].

Kaempferol (**9**) inhibited cell proliferation and colony formation capacity in MCF-7 cells. It also induced apoptosis, evidenced by chromatin condensation and nuclear fragmentation, poly (ADP-ribose) polymerase (PARP) cleavage, BCL-2 down-regulation and BAX induction [43]. The effects of kaempferol (**9**) on ERα in MCF-7 cells are intricate [44], as it induces the degradation of ERα and prevents E2-induced cell proliferation [45]. In a luciferase assay, kaempferol (**9**) activated the transcription of the E2-responsive reporter gene transfected into MCF-7 cells in the absence of E2, although high concentrations ($<10^5$ M) of kaempferol (**9**) reduced luciferase activity; in the presence of E2, luciferase activity was blocked by 10^5 M kaempferol [46]. Kaempferol (**9**) was later shown to repress E2-or triclosan-induced MCF-7 cell growth *via* the non-genomic ERα signaling pathway associated with IGF-1R; kaempferol (**9**) revealed an anti-estrogenic effect by down-regulating phosphorylated insulin receptor substrate-1 (pIRS-1), pAKT, phosphorylated mitogen-activated protein kinase kinase (pMEK)1/2 and pERK1/2, the main proteins in IGF-1R signaling which are induced by E2. *In vivo*, in *nude* mice inoculated with MCF-7 cells, the combination of kaempferol (**9**) and E2 significantly reduced tumor volume as compared to single E2 treatment. Furthermore, tumor sections from kaempferol (**9**)- and E2-treated animals showed considerably lower expression of proliferating cell nuclear antigen (PCNA) and cyclin D1 but higher expression of BAX, as compared to E2 treatment [47].

Chalcone (**10**) and licochalcone A (**11**) produced cytotoxicity in MCF-7 cells, as evaluated through lactate dehydrogenase (LDH) leakage to determine plasma membrane damage. Forty-eight-hour treatment with licochalcone A (**11**) showed LDH activity for concentrations higher than the IC_{50}; in fact, both chalcone (**10**) and licochalcone A (**11**) produced high LDH leakage at IC_{80}. Both chalcones caused cell cycle arrest in G1 as compared to controls, with a reduction in the proportion of cells in the S and G2/M phases. Furthermore, apoptosis percentages at IC_{50} were 72% and 85% for licochalcone A (**11**) and chalcone (**10**), respectively. In particular, chalcone (**10**) at IC_{50} resulted in a large proportion of cells in

late apoptosis. Both chalcones reduced BCL-2 and cyclin-D1 expression, promoting BAX expression and PARP cleavage. Finally, chalcone (**10**) induced the expression of the cell death-inducing DNA fragmentation factor alpha subunit-like effector A (*CIDEA*) gene (by affecting its promoter activity) and CIDEA protein expression [48].

Compound **12** (named LW-214 by the authors) is a synthetic flavonoid which shows improved water solubility attributed to a polar group on C8 and enhanced stability resulting from a hydrophobic substituent on C7. After 24 h-treatment, MCF-7 cells showed a decrease in BCL-2 expression and an increase in BAX, with PARP and caspase-9 cleavage and reactive oxygen species (ROS) generation. In addition, cytochrome *c* levels decreased in mitochondria but increased in the cytosol, and AIF translocated from the mitochondria to the nucleus causing DNA fragmentation and chromatin condensation. Compound **12** increased pJNK, while pre-treatment with a JNK inhibitor partially reversed these pro-apoptotic effects, reducing BAX and increasing BCL-2. Moreover, compound **12** down-regulated thioredoxin (TRX-1), whose reduced form (cytosolic form of TRX) interacts with the N-terminal portion of apoptosis stimulating kinase 1 (ASK1). Compound **12** down-regulated TRX-1 expression and caused a dissociation of ASK1 from TRX-1, which switches the inactive form of ASK1 to the active pASK, thus promoting apoptosis. *In vivo*, compound **12** showed inhibitory effects on tumor growth in MCF-7 cells inoculated in *nude* mice, as TUNEL assays in tumor tissues showed increased staining intensity correlated with DNA damage. Immunohistochemical assays for TRX-1 revealed positive staining in tumors obtained from control mice but low staining in the compound **12**-treated group. In sum, compound **12** induced apoptosis *in vitro* and *in vivo* by decreasing TRX-1 in luminal breast cancer models [49].

Compound **13** (named aminoflavone NSC 686288 by the authors) demonstrated anti-proliferative activity in MCF-7 cells through a mechanism involving AhR. Flavones, flavonols, flavanones and isoflavones are the main subclasses of flavonoids reported as AhR modulators [50,51] with anti-neoplastic potential [52]. Loaiza-Perez and collaborators demonstrated that compound **13** produced MCF-7 cell apoptosis, promoting the translocation of AhR to the nucleus and its binding to xenobiotic response element (XRE) sequences of CYP1A1 and CYP1B1 promoters to induce their transcription. *In vivo*, *nude* mice inoculated with MCF-7 cells showed tumor growth inhibition upon compound **13** intraperitoneal administration [53]. Compound **13**-mediated anti-cancer activity has been linked to ROS production and oxidative DNA damage, inducing DNA-protein cross-links, DNA single-strand breaks, and histone H2AX phosphorylation [54]. The compound **13** derivative, pro-drug AFP464, has undergone evaluation in clinical trials (Table 4) and also exhibited cytotoxicity in MCF-7 cells and in murine ER-positive LM05 breast cancer cells, both in an AhR-dependent fashion [55].

In line with these findings, we have synthetized different flavone derivatives and compared them with natural flavonoids, demonstrating strong MCF-7 cell growth inhibition by synthetic 2′-nitroflavone (**14**) [56]. Moreover, we observed that 2′-nitroflavone (**14**) exerted apoptotic effects *in vitro* and *in vivo* in HER2-positive LM3 murine breast tumor cells [57].

3.1.2. Flavonoids as inhibitors of luminal breast cancer cell migration and invasion

The backbone flavone, the core structure of flavonoids, has been shown to inhibit migration in MCF-7 cells [58]. For instance, a pentamethoxylated flavone (**15**) (5,3′-dihydroxy-3,6,7,8,4′-pentamethoxyflavone) decreased MCF-7 cell motility in wound-healing assays. In addition, this pentamethoxylated flavone (**15**) inhibited NF-κB p65 and BCL-2 protein expression but increased that of BAX and cytochrome *c*. Moreover, it induced ROS generation and up-regulated p53 and p21 protein levels. In summary, NF-κB inhibition by this flavone (**15**) in MCF-7 cells has been postulated to contribute to the suppression of cell migration and proliferation, probably through the regulation of intrinsic apoptosis [59].

Puerarin (**16**), an 8-*C*-glucoside of daidzein, also affects the NF-κB pathway. MCF-7 cells exposed to LPS showed greater migration ability than control cells, while co-treatment with puerarin (**16**) reduced cell migration in a concentration-dependent manner. The mRNA expression of chemokine receptors C–C chemokine receptor type 7 (CCR7) and C-X-C chemokine receptor type 4 (CXCR-4) increased remarkably in MCF-7 cells treated with LPS, an effect offset by co-treatment with puerarin (**16**). Regarding invasive capacity, LPS increased MCF-7 cell invasion and up-regulated metalloproteinase (MMP)-2 and −9 mRNA expression, while puerarin (**16**) again blocked these effects. Puerarin (**16**) also reduced LPS-induced cell adhesion to collagen I, collagen IV and fibronectin. In addition, the mRNA and protein expression of vascular adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), TNFα and IL-6 increased in LPS-treated cells but decreased upon flavonoid co-treatment. Moreover, pre-stimulation of MCF-7 cells with LPS triggered the phosphorylation of NF-κB p65, NF-κB inhibitor (IκBα) and ERK1/2 which was all reversed by co-treatment with puerarin (**16**) [60].

Calycosin (**17**) also inhibited MCF-7 and T47D cell migration in wound-healing assays, while higher doses of this compound significantly reduced cell invasion in a concentration-dependent manner. Also, forkhead box P3 (FOXP3) mRNA and protein levels were markedly reduced in MCF-7 and T47D cells. Previous studies have linked FOXP3 expression to MMP-9 and VEGF signaling, with important roles in tumor invasion and metastasis [61]. Calycosin (**17**) treatment was also demonstrated to reduce mRNA and protein levels of MMP-9 and VEGF in both MCF-7 and T47D cells [62]. Similarly, orientin (**18**), luteolin 8-*C*-β-D-glucopyranoside, has shown anti-migratory action, as increased MCF-7 cell mobility induced by tetradecanoyl-phorbol acetate (TPA) was prevented by flavonoid pre-treatment. Invasiveness was also attenuated by orientin (**18**) in MCF-7 cells; flavonoid treatment promoted a reduction in MMP-9 activity and mRNA expression after TPA induction. Furthermore, orientin (**18**) reduced IL-8 mRNA expression and secretion to conditioned media supported by TPA, blocked TPA-mediated membrane translocation of PKCα and ERK phosphorylation and attenuated the nuclear translocation of c-JUN, c-FOS and STAT3 promoted by TPA. To sum up, ERK seems to be an upstream mediator of MMP-9 and IL-8 in TPA-induced MCF-7 cells while orientin (**18**) blocks these pathways and attenuates cell invasiveness [63].

Corylin (**19**) showed inhibitory effects on MCF-7 cell migration and invasion in wound-healing and transwell assays, respectively, and reduced proliferation rates. In addition, this flavonoid induced miR-34c in MCF-7 cells, which was partly abolished after p53 knock-down. Moreover, the long non-coding (lnc) RNA LINC00963 was predicted as a miR-34c target, and LINC00963 mRNA expression was reduced after transfection with miR-34c mimics in MCF-7 cells. Importantly, corylin (**19**) decreased LINC00963 expression while its inhibitory effect on cell migration and invasion was abolished by LINC00963 over-expression. Therefore, corylin (**19**) may be thought to impact the miR-34c/LINC00963 axis to regulate MCF-7 cell migration [64].

Hinokiflavone (**20**) has proven to be a potent inhibitor of MMP-9, as observed in pharmacophore-based molecular docking and dynamic simulation studies. *In silico* studies with hinokiflavone (**20**) from *Juniperus communis* showed a binding free energy of −26.54 kJ/mol (as high as that exhibited by other known MMP-9 inhibitors), targeting the MMP-9 S1 pocket [65]. In MCF-7 cells, MMP-9 inhibition in the presence of hinokiflavone (**20**) was confirmed through gelatin zymography and gelatinolytic inhibition assays. MTT cytotoxicity studies with MCF-7 cells rendered an IC_{50} value of 43 μM after 48 h-incubation. Thus, the inhibition of metastasis-specific MMP-9 in breast cancer cells by certain flavonoids might be considered a target for their anti-cancer action [65].

3.1.3. Roles of flavonoids in epithelial-mesenchymal transition reversion

EMT, a key event for tumor cell dissemination, is a process involving the loss of cellular epithelial features and polarity and the acquisition of a mesenchymal phenotype. EMT is characterized by a reduction in epithelial cell-surface markers E-cadherin, occludin and zonula occludens-1 (ZO-1), as well as the up-regulation of mesenchymal markers

N-cadherin and vimentin, extracellular matrix protein fibronectin and EMT-activating transcription factors SNAIL, SLUG, TWIST and ZEB [66]. Activated wingless-type MMTV integration site family (WNT)/β-catenin signaling is associated with reduced E-cadherin levels, increased metastatic risk, and a poor clinical outcome for cancer patients [67,68]. Other signaling pathways such as NOTCH are also involved in EMT; NOTCH signaling is often aberrantly over-expressed in many cancers and increases the expression of SNAIL, TWIST and SLUG in epithelial cells to promote EMT [69].

The flavonol 3,6-dihydroxyflavone (**21**) reduced the levels of mesenchymal markers SNAIL, TWIST, SLUG and N-cadherin and increased the levels of epithelial marker E-cadherin in MCF-7 cells. In addition, the induction of SNAIL, TWIST, SLUG and N-cadherin and the down-regulation of E-cadherin mediated by transforming growth factor-β (TGF-β) were effectively mitigated by 3,6-dihydroxyflavone (**21**) co-treatment. In addition, 3,6-dihydroxyflavone (**21**) also suppressed NOTCH signaling pathway in MCF-7 cells, causing the down-regulation of NOTCH1, intracellular domain of NOTCH (NICD) and NOTCH target genes. Moreover, significantly less NICD was isolated in the NICD-protein mastermind-like-1 (MAML) transcriptional complex, which indicates NOTCH signaling inactivation [70]. In a rat breast carcinogenesis model, 3,6-dihydroxyflavone (**21**) was further shown to induce apoptosis, probably by up-regulating the expression of pro-apoptotic miR-34a (a transcriptional target of p53) and reducing anti-apoptotic miR-21 [71].

Compound **22** (named LFG-500 by the authors) was formulated to overcome first-pass metabolism which would most likely happen at the hydroxyl groups of most flavonoids. Therefore, this compound was designed to improve oral bioavailability by introducing a piperazine and a benzyl group at positions 6 and 7 of baicalein (compound **47**) [72]. Compound **22** suppressed EMT in lung adenocarcinoma cells within an inflammatory microenvironment [73]. In MCF-7 cells, the anti-EMT activity of compound **22** was investigated after TGF-β induction; TGF-β decreased the expression of ZO-1 and E-cadherin and increased N-cadherin and vimentin, while compound **22** reversed these changes. Furthermore, the expression of SNAIL and SLUG was also down-regulated by compound **22**. EMT repression by compound **22** was associated with the HIPPO/Yes-associated protein (YAP) signaling pathway, as increased phosphorylation levels of kinases mammalian STe20-like 1 and 2 (MST1/2) and large tumor suppressor kinase 1 (LATS1) produced increased YAP phosphorylation. In fact, a decrease in total YAP level and an increase in pYAP expression were observed in MCF-7 cells treated with compound **22**. Treatment also remarkably reversed TGF-β-induced nuclear localization of YAP and suppressed the transcriptional activity of the YAP/TEA domain transcription factor 1 (TEAD) complex, as demonstrated in luciferase reporter assays. Thus, compound **22** stimulated HIPPO signaling, leading to the repression of YAP activity through its phosphorylation. Cells transfected with YAP showed enhanced expression of SNAIL and vimentin and down-regulated expression of E-cadherin, both effects abolished by compound **22**. Furthermore, the compound also down-regulated integrin-linked kinase (ILK). Finally, compound **22** treatment dramatically inhibited tumor growth and lung metastasis in MMTV-PyMT transgenic mice with early breast carcinomas, yielding decreased levels of YAP/ILK and high levels of pYAP [74].

The synthesis of chalcones on 2-methoxyestradiol (2ME2) has produced highly active compounds [75], promising for luminal breast cancer therapy. Indeed, 2ME2, an endogenous metabolite of estradiol formulated as Panzem™ Nanocrystal Colloidal Dispersion, has been tested as an anti-tumor agent in phase I/II clinical trials for multiple myeloma, glioblastoma, ovarian and prostate cancers [76]. Additionally, 2ME2 has shown cytotoxic effects by targeting tubulin polymerization through its binding at the colchicine binding site while inhibiting MCF-7 cell proliferation at IC_{50} 2.5 μM for 72 h. Compound **23**, one of these chalcone-modified estradiol analogs named compound 11e by the authors, significantly reduced blood vessel formation in chick chorioallantoic membrane assays, resembling the anti-angiogenic effect of 2ME2 [75], and inhibited MCF-7 cell proliferation at IC_{50} 70 μM for 72 h. Regarding EMT in MCF-7 cells, compound **23** increased the expression of ZO-1 and E-cadherin and reduced that of N-cadherin and vimentin, which indicates EMT inhibition. *In vivo,* an intraperitoneal injection of compound **23** inhibited tumor growth in *nude* mice inoculated with MCF-7 cells; tumor weight and volume were reduced, while body weights gradually increased during treatment. In contrast, mice inoculated with 2ME2 showed body weight loss indicative of toxicity [75].

Hispidulin (**24**) also blocked EMT in MCF-7 cells, significantly increasing the mRNA and protein expression of E-cadherin and occludin. Moreover, hispidulin (**24**) suppressed TGF-β_1-induced EMT, as TGF-β_1 and hispidulin (**24**) co-treatment produced higher E-cadherin protein expression than single TGF-β_1 treatment. As previously demonstrated, TGF-β_1 induces EMT upon its interaction with transmembrane kinase receptors, causing SMAD2, SMAD3 or SMAD4 activation [77]. TGF-β_1 and hispidulin (**24**) co-treatment also significantly inhibited SMAD2/3 phosphorylation in MCF-7 cells, while TGF-β_1 alone increased pSMAD2/3. In addition, migration was significantly suppressed in MCF-7 cells treated with TGF-β_1 and hispidulin (**24**) as compared to those only treated with TGF-β_1 [78].

Calycosin (**17**) has also inhibited EMT in colon cancer cells [79]. Moreover, calycosin (**17**) suppressed migration and invasiveness through EMT inhibition in T47D and MCF-7 cells, increasing the expression of E-cadherin and reducing N-cadherin, vimentin, CD147, MMP-2 and -9, in contrast to TGF-β_1 treatment [80]. The basic leucine zipper ATF-like transcription factor (BATF) family, which belongs to the AP-1/ATF super-family of transcription factors, acts as an inhibitor of AP-1 activity and has been proven to inhibit EMT by down-regulating TGF-β_1 [79]. Of note, calycosin (**17**) down-regulated BATF mRNA and protein levels in T47D and MCF-7 cells and inhibited migration and invasiveness in BATF-over-expressing T47D cells *via* BATF/TGF-β_1. *In vivo*, calycosin (**17**) delayed tumor growth in *nude* mice subcutaneously inoculated with T47D cells, with a sharp reduction in tumor volume and weight [80].

Compound 2′-hydroxyflavanone (**25**) inhibited breast cancer cell growth *in vitro* and *in vivo* [81,82]. Most importantly, studies of bioinformatics have shown 2′-hydroxyflavanone (**25**) docking to ligand binding sites of ERα and the non-ATP binding cassette (ABC) transporter Ral-interacting protein (RLIP76), as well as to the ATP binding pocket of HER2. Moreover, 2′-hydroxyflavanone (**25**) down-regulated ERα and enhanced the inhibitory effects of imatinib mesylate (a kinase inhibitor) in MCF-7 cells. RNA-Seq analysis showed that 2′-hydroxyflavanone (**25**) strongly modified the global pattern of gene expression in ER-positive MCF-7, HER2-positive SKBR3 and TNBC MDA-MB-231 cells, for example, causing inhibition of ERα and octamer-binding transcription factor (OCT)-4 canonical pathways [83]. In addition, in MCF-7 cells, 2′-hydroxyflavanone (**25**) reduced the expression of vimentin, Ki67, CD31, survivin and BCL2, inhibited AKT phosphorylation, and increased the expression of E-cadherin, BAX and cleaved PARP. Also in MCF-7 cells, 2′-hydroxyflavanone (**25**) exerted anti-migratory and anti-invasive action and lowered RLIP76 protein expression. *In vivo*, *nude* mice bearing MCF-7 cell xenografts treated with either 2′-hydroxyflavanone (**25**) or with RLIP76 antisense rendered lower tumor weight than the corresponding controls. In addition, analysis of tumor tissues from control and treated mice showed that 2′-hydroxyflavanone (**25**) decreased vimentin and RLIP76 protein expression levels but increased E-cadherin expression [82].

Kaempferol (**9**) produced EMT inhibition by reducing N-cadherin, SNAIL, SLUG, vimentin and ZEB in non-small cell lung cancer cells [84]. The compound also suppressed TGF-β_1-induced migration and EMT by abrogating MMP expression and increasing E-cadherin expression [85]. Kaempferol (**9**) was also demonstrated to inhibit invasion of human breast carcinoma cells by down-regulating MMP-9 expression and activity [86]. In MCF-7 cells, inhibition of ERα expression and function by kaempferol (**9**) has been well-documented; for instance, kaempferol (**9**) inhibited the expression of E2-dependent genes such as insulin receptor substrate 1 (*IRS-1*), cyclin D1 and PR [45]. Molecular docking and dynamic studies demonstrated kaempferol (**9**) interaction with ERα and

showed its estrogenic potential, although more studies are required to establish it as a selective estrogen receptor modulator (SERM) [87]. In MCF-7 cells, E2 induced EMT by down-regulating E-cadherin and up-regulating N-cadherin, SNAIL and SLUG protein expression. Conversely, kaempferol (**9**) effectively inhibited EMT induced by E2, as co-treatment reduced N-cadherin, SNAIL and SLUG protein expression to control levels. However, kaempferol (**9**) alone failed to induce significant effects on EMT reversion. Furthermore, E2 also increased cathepsin D and MMP-9/-2 protein expression, while co-treatment with kaempferol (**9**) restored both protein expressions to control levels. Finally, kaempferol (**9**) prevented E2-induced MCF-7 cell invasion [88].

3.1.4. Anti-angiogenic actions of flavonoids in luminal breast cancer

Various flavonoids have been associated with the inhibition of angiogenesis in breast cancer [89–92]. Quercetin (**3**) has been repeatedly implicated in anti-angiogenesis by reducing serum VEGF levels in tumor-bearing animals [93], inhibiting VEGF secretion in MCF-7 cells [94] and blocking calcineurin (a calcium- and calmodulin-dependent serine-threonine phosphatase), which dephosphorylates the nuclear factor of activated T cells (NFAT) to induce its nuclear translocation [90]. Fluorescence spectroscopy and molecular docking studies have shown direct interaction of quercetin (**3**) with calcineurin; indeed, three potential binding sites for quercetin (**3**) have been found in a region between the active center of calcineurin subunits A and B, a similar binding area to that of cyclosporin A and tacrolimus [95]. Therefore, quercetin (**3**) has been proposed as a non-competitive calcineurin inhibitor, a role which has also been previously suggested for kaempferol (**9**) [96]. *In vivo*, in *nude* mice inoculated with MCF-7 cells, quercetin (**3**) was compared to tacrolimus (a calcineurin inhibitor which blocks the calcineurin/NFAT pathway), and both treatments significantly decreased tumor volume and weight, promoting tumor necrosis. Ki67 tumor staining was also significantly reduced in quercetin- and tacrolimus-treated mice. Worth highlighting, von Willebrand factor (vWF) immunohistochemical staining was lower in tumors from quercetin- and tacrolimus-treated *versus* vehicle-treated mice, which suggests that quercetin (**3**) reduces tumor microvessel density; serum VEGF levels also significantly decreased in both treatment groups. Moreover, quercetin (**3**) inhibited calcineurin activity, as determined by a dephosphorylation assay performed in tumor homogenates. In addition, tumor VEGF, VEGFR2 and NFATc3 protein and gene expression were down-regulated by quercetin (**3**). Thus, this flavonoid inhibited angiogenesis in MCF-7 cell xenografts in *nude* mice, which was associated with the suppression of calcineurin activity and its regulated pathways [97]. Recently, quercetin (**3**) has been also postulated to inhibit angiogenesis by down-regulating MALAT1 and MIAT lncRNAs in human umbilical vein endothelial (HUVEC) cells [98].

Wogonoside (**26**) is an *in vivo* metabolite of wogonin (**44**) with the presence of 7-glucuronic acid. In MCF-7 cells, wogonoside (**26**) reduced VEGF protein and mRNA expression as well as secretion. In tube formation assays, compared with MCF-7 cell-derived conditioned medium alone, wogonoside (**26**) resulted in the inhibition of tube-like structures in HUVEC cells. Similarly, vessel sprouting in rat aortic ring was significantly stimulated by conditioned media from tumor cells, an effect offset by co-treatment with wogonoside (**26**). Worth pointing out, the anti-angiogenic actions of wogonoside (**26**) at the concentrations tested were not due to loss of viability or apoptosis in MCF-7 cells. *In vivo*, wogonoside (**26**) inhibited tumor growth in MCF-7 cell xenografts in *nude* mice and reduced tumor vascular density, as revealed by CD31 immunohistochemical staining. Moreover, VEGF and β-catenin protein expression was also decreased in lysates of tumor tissues. In mechanistic studies, wogonoside (**26**) was shown to inhibit nuclear accumulation of β-catenin and its DNA binding capacity in MCF-7 cells, therefore reducing WNT/β-catenin pathway activation [99].

Luteolin (**4**) inhibited the secretion and mRNA expression of VEGF in T47D cells treated with the synthetic progestin medroxyprogesterone acetate (MPA). *In vivo*, luteolin (**4**) blocked progestin-induced T47D tumor growth in *nude* mice. In addition, mice co-treated with MPA and luteolin (**4**) demonstrated significantly reduced tumor blood-vessel density as compared to single MPA administration, as shown by CD31 immunohistochemistry. In this xenograft model, tumor VEGF expression was also significantly reduced by co-treatment. Furthermore, luteolin (**4**) blocked the MPA-induced acquisition of stem cell-like properties by breast cancer cells, as determined by CD44 expression, aldehyde dehydrogenase activity and mammosphere formation assays [31,100].

Flavonoid precursor 4-hydroxychalcone (**27**) showed anti-angiogenic properties *in vitro*, inhibiting HUVEC cell proliferation and VEGF-induced migration and tubulogenesis [101]. Other chalcones such as flavokawain A (**28**) from kava extracts have also shown anti-angiogenic effects [89]. In tubulogenesis assays, the number of tubes formed by HUVEC cells was shown to decline with increasing doses of flavokawain A (**28**). In *ex vivo* assays of rat aortic ring, vessel outgrowth was blocked in the fragmented aorta. Moreover, flavokawain A-treated MCF-7 cells exhibited a reduction in the level of p27, polo-like kinase 1 (PLK1) and forkhead box M1 (FOXM1), and an increase in the levels of p21, BAX and cytochrome *c* [102]. Flavokawain B (**29**) also inhibited HUVEC cell tube formation *in vitro*, as well as reduced vessel sprouting *ex vivo* in rat aortic ring [103] and *in vivo* in a zebrafish model [104], and showed cytotoxic effects on MCF-7 cells [105]. Other synthetic chalcone derivatives containing a pyrazole ring have also demonstrated cytotoxicity against MCF-7 cells and essential inhibition of tumor cell-induced neovascularization. A significant decrease in VEGF mRNA expression was detected in MCF-7 cells treated with compounds **30A** and **B** (named chalcones 3 and 5, respectively, by the authors); compound **30B** revealed a more potent effect than **30A**, probably because of its 1,3-indandione group as compared to the benzothiazole group of compound **30A**. Furthermore, compounds **30A** and **B** produced an appreciable decline in BCL-2 protein levels, induced caspase-8 activation, and increased p53 expression in MCF-7 cells [106].

Jaceidin (**31**) and compound **32** (named compound 3 by the authors) isolated from *Chiliadenus montanus* exhibited cytotoxic effects on MCF-7 cells in comparison to doxorubicin. *In silico* and molecular docking studies suggested that jaceidin (**31**) was a selective inhibitor of VEGFR. Strong docking scores of −9.02 and −8.96 kJ/mol were calculated for jaceidin (**31**) and compound **32**, respectively, while quercetin (**3**) and genistein (**33**), two flavonoids known to inhibit angiogenesis, rendered scores of −8.96 and −8.83 kJ/mol, respectively. Angiogenesis inhibitor pazopanib showed extra H-bonding to VEGFR, giving it a better docking score of −9.5 kJ/mol. The authors thus postulated that structural modifications of these flavonoids through the addition of extra H-bonding donors and/or acceptor on the phenyl ring could reinforce their binding to VGFR [107].

3.2. Flavonoids in triple-negative breast cancer

TNBC comprises mammary gland tumors negative for PR, ER and HER2, which constitute about 15–20% of breast cancer [15,16]. TNBC patients generally reveal signs of poor prognosis due to unfavorable characteristics in histologic grade, metastasis and tumor size. Despite a common shared gene expression pattern, molecular analyses show that TNBC is a highly heterogeneous disease and was therefore further subclassified using gene profiles [108]. Some effects of simple natural and synthetic flavonoids on TNBC and the potential underlying mechanisms are described in the following sections and summarized in Table 3. IC_{50} values of flavonoids and some common antitumor agents are included in Table 3 to compare their relative antitumor potency mainly in MDA-MB-231 cells.

3.2.1. Effects of flavonoids on cell cycle arrest, inhibition of proliferation and apoptosis induction

Genistein (**33**) was shown to inhibit human TNBC MDA-MB-231 cell proliferation at concentrations of 5–20 μM in 24–72 h MTT assays. Moreover, genistein (**33**) induced apoptosis on these cells, as revealed by annexin V/PI staining, with apoptosis percentages of 6.78, 18.98, 30.45

Table 3
Effects of some flavonoids on triple-negative breast cancer.

Flavonoid	CELL CYCLE, PROLIFERATION, APOPTOSIS		Human cell lines IC_{50} (μM)	*In vivo*[a]	Ref.
	Accumulation/increase	**Down-regulation/inhibition/reduction**			
Genistein (**33**)	G2/M phase arrest	NF-κB; NOTCH-1 pathway; cyclin B1, BCL-2; BCL-XL	MDA-MB-231 *(10)****	nd	[109]
Calycopterin (**34**)	sub-G1 phase; BAX; caspases-8 and -3	BCL-2	MDA-MB-231 *(150)***	nd	[110]
Tangeretin (**35**)	G2/M phase arrest; BAX; caspase-3, -8 and -9	BCL-2; cyclin-B1; cyclin-D	MDA-MB-231 *(9)**	nd	[111]
Fisetin (**36**)	caspase-8 and −9 activation; cleaved PARP-1	decrease in G1 cell cycle percentage	MDA-MB-231 *(100)**** MDA-MB-468	nd	[113]
Naringenin (**37**)	BAX; caspase-3 and -9 activation	BCL-2; pSTAT3	MDA-MB-231 *(>200)***	nd	[114]
Isorhamnetin (**38**); Genkwanin (**39**); Acacetin (**40**)	G2/M phase arrest; cleaved caspase-3; p53; p62 degradation; autophagy	pCDC2; cyclin B1; BCL-2; BCL-XL; total PARP-1; PI3Kγ activity; pAKT/pmTOR/p70S6K/pULK	MDA-MB-231 *(56)**; *(59)**; *(83)**	nd	[115]
	DOCKING Target: PI3Kγ (inhibition)				
Icariin (**41**)	cleaved caspase-3; BAX; ROS; infiltrating T cells	BCL-2; NF-κB nuclear translocation; PDL-1; MDSCs cells	MDA-MB-231 *(>15)*** MDA-MB-453 4T1	*Nude*/ MDA-MB-231; Balb/c/ 4T1	[116]
Sophora-flavanone G (**42**)	nuclear condensation; fragmented DNA; cleaved caspase-8, -3, and -9; cleaved PARP-1; BAX; ROS	BCL-2; BCL-XL	MDA-MB-231 *(30)**	nd	[117]
Luteolin (**4**)	cleaved caspase-8, -9 and -3; cleaved PARP-1; FAS; BAX	BCL-XL; mitochondrial transmembrane potential	MDA-MB-231 *(>40)**	nd	[118]
	IN SILICO/Natural products enriched DNA-encoded chemical libraries (nDELs) Target: PARP-1				[119]
Oroxin A (**43**)	β-Gal activity; ROS; endoplasmic reticulum stress; senescence; GRP78; ATF4; P38 phosphorylation	F-actin microfilaments; tubulin network: less cytoplasm distribution	MDA-MB-231 *(16)****	nd	[120]

Flavonoid	CELL MIGRATION & INVASION		Human cell lines IC_{50} (μM)	*In vivo*[a]	Ref.
	Promotion/up-regulation	**Down-regulation/inhibition**			
Wogonin (**44**)		IL-8; MMP-9; Matrigel™ invasion assay; 5-LO; BLT2; pERK	MDA-MB-231 *(nd)*	*Nude*/ MDA-MB-231	[121]
Silibinin (**8**)	mitochondrial fusion; OPA1; MFN1; MFN2	wound closure; transwell migration; F-actin stress fibers; Matrigel™ invasion assay; MMP-2; MMP-9; paxillin; ROS; NLRP3 inflammasome	MDA-MB-231 *(>225)**	nd	[123]
Luteolin (**4**)		MMP-9; transwell migration; Matrigel™ invasion assay	MDA-MB-231 *(>40)**	nd	[118]
Apigenin (**2**)		transwell migration; Matrigel™ invasion assay; IL-6	MDA-MB-231 *(nd)*	*Nude*/ MDA-MB-231	[124]
Myricetin (**45**)		wound-healing; transwell migration; MMP-2/MMP −9 activity	MDA-MB-231Br *(40)*** 4T1	Balb/c/ 4T1	[127]
Formononetin (**46**)	TIMP-1; TIMP-2	MMP-2; MMP-9; pAKT; pPI3K	MDA-MB-231 *(>160)** 4T1	*Nude*/ MDA-MB-231	[129]
Baicalein (**47**)		transwell migration; Matrigel™ invasion assay; MMP-2; MMP-9; pAKT; pERK; pP38; pJNK	MDA-MB-231 *(nd)*	nd	[131]
Proanthocyanidin (**48**)		MMP-9; uPA; uPAR; PAI-1; collagenase activity; IL-6; ICAM-1	MDA-MB-231 *(>337.5)***	nd	[132]
Compound **49**		wound closure; transwell migration uPA; PAI-1; MMP-2; MMP-9; pERK; pP38; NF-κB	MDA-MB-231 *(54)***	nd	[133]

Flavonoid	EPITHELIAL-MESENCHYMAL TRANSITION		Human cell lines IC_{50} (μM)	*In vivo*[a]	Ref.
	Up-regulation	**Down-regulation/reduction**			
Fisetin (**36**)		F-actin polymerization; PI3K-AKT-GSK-3β	MDA-MB-231 *(100)**** BT-549	*Nude*/ MDA-MB-231	[134]
Taxifolin (**50**)	E-cadherin; claudin	N-cadherin; vimentin; F-actin polymerization; SLUG; SNAIL; β-catenin	MDA-MB-231 *(>100)**** 4T1	Balb/c/ 4T1	[135]
Baicalin (**51**)	E-cadherin; claudin	N-cadherin; vimentin; SNAIL; SLUG	MDA-MB-231 *(>100)**** 4T1	Balb/c/ 4T1	[136]

(*continued on next page*)

Table 3 (*continued*)

Luteolin (**4**)	E-cadherin; claudin	N-cadherin; vimentin; SLUG; β-catenin	MDA-MB-231 BT-549 *(nd)*	*Nude*/ MDA-MB-231	[137, 138]
Luteolin (**4**)	E-cadherin	fibronectin; N-cadherin; vimentin; YAP/TAZ (proteosome-degradation)	MDA-MB-231 *(40)*** 4T1	Balb/c/ 4T1	[139]
Cardamonin (**52**)	E-cadherin	vimentin; SNAIL; SLUG	BT-549 *(>15)***	Balb/c/ 4T1	[140]
Apigenin (**2**)		SNAIL; N-cadherin; IL-6	MDA-MB-231 *(nd)*	*Nude*/ MDA-MB-231	[124]
Flavonoid	**ANGIOGENESIS**		**Human cell lines** IC_{50} *(μM)*	***In vivo***[a]	**Ref.**
	Promotion	**Inhibition/reduction**			
Glabridin (**53**)	$\alpha_v\beta_3$ integrin proteosome degradation; SRC inactivation	tubulogenesis; EC migration; pFAK; pAKT; pERK	MDA-MB-231 *(>10)*** HUVEC	*Nude*/ MDA-MB-231	[143]
Isoliquiritigenin (**55**)		tubulogenesis; VEGF; pVEGFR2; MMP-2; tumor microvessel density	MDA-MB-231 *(40)*** HUVEC	*Nude*/ MDA-MB-231	[145]
Wogonoside (**26**)		tubulogenesis; VEGF; GLI1; SMO	MDA-MB-231 *(>200)*** MDA-MB-468 HUVEC	*Nude*/ MDA-MB-231	[146]
Compound **56**		F-actin stress fibers; tubulogenesis; EC migration; EC invasion; CXCL12 secretion; CXCR7 expression	MDA-MB-231 *(>6)*** EA.hy 926	*Nude*/ MDA-MB-231	[148]
Myricetin (**45**)		tumor microvessel density; VEGF secretion; VEGFR2; pP38/P38 in EC	MDA-MB-231 *(>100)*** 4T1 HUVEC	Balb/c/ 4T1	[149]

*Half-maximal inhibitory concentration (IC_{50}) after 24 h-treatment.
**IC_{50} after 48 h-treatment.
***IC_{50} after 72 h-treatment.
****IC_{50} after 96 h-treatment. For comparison, IC_{50} (μM) for MDA-MB-231 cells after 48 h-treatment with doxorubicin, paclitaxel, docetaxel, cisplatin, dasatanib and 5-fluorouracil are: 3.16 [171], 0.008 [174], 0.037 [175], 21.3 [173], 0.014 [174] and 2.202 [174], respectively.
[a] Mice/cell line inoculated. nd: not determined. EC: endothelial cell.

and 60.64% for 0, 5, 10 and 20 μM, respectively. Genistein (**33**) induced accumulation in the G2/M phase of the cell cycle, with concentrations of 0, 5, 10 or 20 μM yielding 4.93, 12.54, 18.93 and 30.95%, respectively. NOTCH-1 protein levels were down-regulated by genistein (**33**) in MDA-MB-231 cells in a dose-dependent manner. This flavonoid also inhibited NF-κB nuclear translocation and down-regulated the expression of NF-κB-targeted proteins such as cyclin B1, BCL-2 and B-cell lymphoma-extra-large (BCL-XL) [109].

Calycopterin (**34**) reduced proliferation and colony formation in MDA-MB-231 cells. PI staining assays showed a cell cycle profile with increasing proportions of sub-G1 phase from 0.6% in the untreated group to 8.2% in IC_{50}-treated cells. Acridine orange and ethidium bromide staining showed that calycopterin (**34**) at IC_{50} increased the percentage of early and late apoptotic cells with fragmented bright nuclei from 5% in untreated cells up to 50% after treatment. In fact, quantification through annexin V/PI analysis revealed that apoptosis in MDA-MB-231 cells treated with the effective concentration of calycopterin (**34**) increased by 50% (47% late apoptosis +3.7% early apoptosis) as compared to control cells (2.9% + 3.8%). Moreover, calycopterin (**34**) induced the mRNA expression of BAX, caspase-8 and -3, but down-regulated that of BCL-2 [110].

Tangeretin (**35**) reduced viability at IC_{50} 9 μM in MDA-MB-231 cells but rendered an $IC_{50} > 100$ μM in normal human breast Hs841.T cells. Early and late apoptotic cell percentages increased with dosage: annexin V/PI staining showed 5% of apoptotic cells in untreated samples and around 69% of apoptotic 18 μM-tangeretin-treated MDA-MB-231 cells. BAX, caspase-3, -8 and -9 protein expression increased in a dose-dependent manner, while BCL-2, cyclin-B1 and -D protein levels were reduced by treatment. Tangeretin (**35**) also caused G2/M arrest in MDA-MB-231 cells [111].

Fisetin (**36**), a well-studied anti-cancer flavone [112], inhibited cell growth (25, 50 or 100 μM) in human TNBC MDA-MB-468 and MDA-MB-231 cells but barely affected normal human mammary epithelial cells. Upon cell culture with 50 μM fisetin (**36**) for 48 h, Oregon Green™ 488 staining showed a reduction in the percentage of MDA-MB-468 cells in the G1 phase and an increase in the percentage of cells in G2/M. MDA-MB-231 cells also exhibited a decrease in the percentage of G1 cells, although the accumulation of cells in S and G2/M was not significant. Annexin V/PI staining unveiled early and late apoptosis induced by fisetin (**36**), MDA-MB-468 cells being more sensitive than MDA-MB-231 cells. Fisetin (**36**) also caused caspase-8, -9 and PARP-1 cleavage [113].

Naringenin (**37**) also induced a dose-dependent reduction in MDA-MB-231 cell survival in MTT assays. Moreover, a significant increase in both late- and early-stage apoptotic cells was observed upon 200 μM naringenin (**37**) treatment for 48 h. Naringenin (**37**) inhibited IL-6-induced modulation of BAX/BCL-2 proteins, reducing BCL-2 expression while inducing BAX and activating caspase-9 and -3. Naringenin (**37**) also reduced STAT3 phosphorylation, without affecting total STAT3 protein expression [114]. Isorhamnetin (**38**), genkwanin (**39**) and acacetin (**40**) derived from *Tephroseris kirilowii* (a perennial herb widely distributed in China) also caused cytotoxicity in MDA-MB-231 cells with IC_{50} values of 55, 58 and 82 μM, respectively, after 24 h. These flavonoids also triggered G2/M phase arrest and a marked decrease in the levels of phosphorylated cell division control protein 2 homolog (CDC2) kinase and cyclin B1. Isorhamnetin (**38**) and genkwanin (**39**) induced apoptosis more potently than acacetin (**40**) but all of them reduced the levels of BCL-2, BCL-XL and total PARP-1 and increased the levels of p53 and cleaved caspase-3. These flavonoids also induced autophagy in MDA-MB-231 cells; treatments resulted in marked augment in

Table 4
Clinical trials with flavonoids in breast cancer.

Flavonoid	Clinical trial	Condition or disease. Inclusion criteria	Study type	Primary objective	Study phase	NCT number and/or reference
Genistein (33)	"Phase 2 Trial of Gemcitabine and Genistein (**33**) in Metastatic Breast Cancer Patients with Biomarker Assays"	Histologically or cytologically confirmed breast cancer. Stage IV disease. Clinical and/or radiological evidence of metastatic disease. (19 participants)	Interventional. Dietary supplement: genistein (**33**). Drug: gemcitabine. Procedure: Tumor biopsy.	Determine the objective response rate in patients with stage IV breast cancer treated with gemcitabine hydrochloride and genistein (**33**).	Phase 2. Recruitment status completed.	NCT00244933
	"Genistein (**33**) in Preventing Breast Cancer in Women at High Risk for Breast Cancer"	At increased risk of developing breast cancer. Prior diagnosis of unilateral *in situ* or invasive breast cancer overall response history of atypical hyperplasia, BRCA 1 and/or BRCA 2 positivity. History of lobular carcinoma *in situ*. No known soy intolerance (126 participants)	Interventional. Drug: genistein (**33**). Other: laboratory biomarker analysis.	Determine the effect of genistein (**33**) on the proliferation of breast epithelial cells obtained by fine needle aspiration in women who are at high risk for breast cancer.	Phase 2. Recruitment status completed.	NCT00290758 [176]
	"Genistein (**33**) in Preventing Breast or Endometrial Cancer in Healthy Postmenopausal Women"	Healthy participants. No history of breast cancer. Not at high-risk for breast cancer. (30 participants)	Interventional. Dietary supplement: Genistein (**33**).	Study the effectiveness of genistein (**33**) on DNA damage and apoptosis in preventing breast or endometrial cancer in healthy postmenopausal women.	Phase 1. Recruitment status completed.	NCT00099008 [177]
AFP464, Aminoflavone (13)	"Study of AFP464 (**13**) ± Faslodex in ER + Breast Cancer"	ER-positive breast cancer patients who had progressed on aromatase inhibitor therapy. (7 participants)	Interventional. Drug: AFP464 (**13**) administered as intravenous infusion. Drug: AFP464 (**13**) administered as intravenous infusion + Faslodex (Fulvestrant).	Clinical benefit response.	Phase 2. Recruitment status terminated.	NCT01233947
	"AFP464 (**13**) in Treating Patients with Metastatic or Refractory Solid Tumors That Cannot Be Removed by Surgery"	Histologic proof of cancer that is now unresectable. Patients with metastatic solid tumors who are refractory to available therapy or for whom standard systemic therapy does not exist. Patients with breast, ovarian, peritoneal or renal cell carcinoma. (68 participants)	Interventional. Drug: AFP464 (**13**) given intravenously. Other: pharmacological study, laboratory biomarker analysis.	Determine the side effects and best dose of AFP464 (**13**) in treating patients with metastatic or refractory solid tumors that cannot be removed by surgery.	Phase 1. Recruitment status completed.	NCT00348699
ME-344 (57), synthetic molecule based on the isoflavan ring structure	"ME-344 (**57**) in Early HER2-negative Breast Cancer with Anti-angiogenic-induced Mitochondrial Metabolism"	Treatment-naïve diagnosed early (stage I-III) HER2-negative breast cancer not candidates for neoadjuvant therapy. (40 participants)	Interventional. Drug: ME-344 (**57**) infused intravenously. Drug: Bevacizumab infused intravenously. Drug: Bevacizumab + ME-344 (**57**) infused intravenously.	Evaluate if the addition of ME-344 (**57**) to anti-angiogenic agents in the cases where the mitochondrial phenotype has been induced enhances anti-tumor activity.	Early Phase 1. Recruitment status completed.	NCT02806817 [167]
Plant extracts	"Intravenous Chemotherapy and Plant-based Dietary Supplements"	Breast cancer patients treated by intra-venous chemotherapy. (200 participants)	Observational. Dietary supplements questionary.	Determine the quantitative impact of the use of dietary supplements by patients with breast cancer and treated in a neo-adjuvant and/or adjuvant condition by IV chemotherapy.	Recruitment status completed.	NCT03959618
	"Does Watercress Intake Have an Impact on Cancer Patients Outcomes?: a Longitudinal Trial"	Long-term effects secondary to cancer therapy in adult breast cancer female patients consecutively referred for primary radiotherapy with curative intent. (200 participants)	Interventional. Dietary supplement: watercress daily during radiation therapy.	Explore the effects of therapeutic diets supplemented with nutraceuticals via watercress that may prove useful in DNA damage modulation, as well as in the global disease prognosis.	Phase 3. Recruitment status unknown.	NCT02468882
S-Equol (58)	"A Pre-surgical Clinical Trial of Therapy With S-equol in Women With TNBC"	Previously untreated TNBC breast cancer determined by a core needle biopsy showing invasive ductal	Interventional. After having a core needle biopsy of the breast confirming TNBC, eligible	To determine if S-equol, an ERβ agonist, is effective in decreasing the proliferation rate of TNBC.	Phase 1. Recruitment status completed.	NCT02352025

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Table 4 (*continued*)

Flavonoid	Clinical trial	Condition or disease. Inclusion criteria	Study type	Primary objective	Study phase	NCT number and/or reference
		carcinoma or invasive lobular carcinoma. (39 participants)	women enrolled on the study will be treated with S-equol at a dose of 50 mg twice daily for 14 days.			

NCT number: ClinicalTrials.gov Identifier.

microtubule-associated protein light chain 3 (LC3) puncta formation, accumulation of LC3-II, and an increase in the levels of autophagy-related gene 5 (ATG5), as well as a decrease in the levels of p62 and the inhibition of PI3K/AKT/mTOR/p70S6K/ULK signaling. Molecular docking revealed that these flavonoids docked in the ATP binding pocket of PI3Kγ and further decreased PI3Kγ kinase activity [115].

Icariin (**41**), a natural flavonol glycoside, exhibited concentration- and time-dependent cytotoxicity in MDA-MB-231 and human TNBC MDA-MB-453 cells as well as murine TNBC 4T1 cells in MTT assays. Annexin V/PI dual-staining after treatment with 10 or 20 μM icariin (**41**) showed apoptotic rates of 26 and 45% for MDA-MB-231 and 13 and 18% for MDA-MB-453 cells, respectively. For 4T1 cells, apoptosis was induced with 20 μM icariin (**41**); moreover, treatment increased the levels of cleaved caspase-3 and BAX but reduced BCL-2, rendering a significantly higher BAX/BCL-2 ratio. Icariin (**41**) dramatically increased ROS in MDA-MB-231 cells, an effect counteracted by pre-treatment with a ROS inhibitor. Although IκBα is degraded when phosphorylated, treatment with icariin (**41**) reduced pIκBα levels in the cytoplasm and NF-κB p65 levels in the nucleus, thus causing NF-κB pathway inactivation. Accordingly, immunofluorescence showed that NF-κB p65 nuclear transportation was inhibited by icariin (**41**) in MDA-MB-231 cells. Most importantly, icariin (**41**) suppressed tumor growth *in vivo*, both in BALB/c mice or BALB/c *nude* mice inoculated with 4T1 cells or MDA-MB-231 cells, respectively. In both tumor models, icariin (**41**) was shown to diminish Ki67 cell staining, and increase cleaved caspase-3, reducing NF-κB and programmed cell death 1 ligand 1 (PD-L1) expression levels. In the mouse 4T1 tumor model, icariin (**41**) also reduced the number of lung metastases. Furthermore, icariin (**41**) attenuated the tumor immunosuppressive microenvironment; tumor infiltrating $CD4^+$ and $CD8^+$ T cells increased after treatment, which dramatically down-regulated the proportion of myeloid-derived suppressor cells (MDSCs) in tumors as compared to controls [116].

Sophoraflavanone G (**42**) produced cytotoxicity in MDA-MB-231 cells treated for 24 h, with an IC_{50} value of 29 μM in MTT assays. Sophoraflavanone G (**42**) also increased nuclear condensation, as shown in DAPI staining, and boosted DNA fragmentation and ROS production. After treatment, MDA-MB-231 cells showed an increase in cell apoptosis, cleaved caspase-8, -3 and -9, cleaved PARP-1 and BAX expression, and a concomitant reduction in BCL-2 and BCL-XL expression, together with the release of more cytochrome *c* from mitochondria to the cytoplasm. Moreover, sophoraflavanone G (**42**) treatment significantly reduced the phosphorylation of AKT (Ser473), P38, ERK1/2 and JNK in MDA-MB-231 cells. Sophoraflavanone G (**42**) also regulated autophagy, promoting LC3-I, LC3-II, ATG5 and beclin 1 and reducing p62 protein expression [117].

Luteolin (**4**) induced apoptosis *via* extrinsic and intrinsic pathways in MDA-MB-231 cells, but luteolin (**4**) glycosides such as luteolin-8-C-β-fucopyranoside, 7-methoxy-luteolin-8-C-β-(6-deoxyxylopyranos-3-uloside) and luteolin-8-*C*-β-D-glucopyranoside produced no cytotoxic effects. Luteolin (**4**) induced early and late apoptosis, as indicated by annexin V^+/PI^- and annexin V^+/PI^+ staining, respectively, in MDA-MB-231 cells. After treatment, the protein levels of caspase-8, -9 and -3 were reduced, whereas their cleaved forms were increased. In addition, luteolin (**4**) treatment promoted an increase in cleaved PARP levels which was inhibited by pre-treatment with pan-caspase inhibitor z-VAD-fmk. Fas antigen (FAS) mRNA expression and BAX protein expression were up-regulated, while BCL-XL protein expression was down-regulated. Luteolin (**4**) also decreased mitochondrial transmembrane potential [118]. Of note, screening in natural products enriched DNA-encoded chemical libraries (nDELs) showed that luteolin (**4**) directly bound to PARP-1, a promising result further confirmed through surface plasmon resonance (SPR). Furthermore, PARP-1 enzymatic activity was blocked by luteolin (**4**) in human MDA-MB-436 TNBC cells, a breast cancer type 1 (BRCA-1)-deficient cell line [119].

Oroxin A (**43**) (baicalein 7-*O*-glucoside) induced endoplasmic reticulum stress-mediated senescence in MDA-MB-231 cells, with cell cycle arrest at the G2/M stage. After treatment, a marked decrease was observed in tubulin and actin networks. In particular, confocal laser microscopy showed tubulin network homogeneously distributed in the cytoplasm of control cells, but more redistribution in the nucleus periphery in treated cells. A similar pattern was induced by oroxin A (**43**) on actin microfilaments. Moreover, oroxin A (**43**) increased β-Gal activity, a classic senescence marker. After treatment, an increase in intracellular ROS levels promoted the expression of endoplasmic reticulum stress markers such as activating transcription factor 4 (ATF4) and glucose-regulated protein with a molecular mass of 78 (GRP78), with increased P38 phosphorylation [120].

3.2.2. *Flavonoids as inhibitors of triple-negative breast cancer cell migration and invasion*

Wogonin (**44**) exerted an inhibitory effect on LPS-enhanced MDA-MB-231 cell invasiveness in Matrigel™-coated transwells. Wogonin (**44**) down-regulated IL-8 and MMP-9 mRNA and protein expression in LPS-stimulated MDA-MB-231 cells and suppressed leukotriene B4 receptor 2 (BLT2) mRNA expression. In addition, wogonin (**44**) treatment markedly attenuated the expression of 5-lipoxygenase (5-LO), its metabolite leukotriene B4 and ERK phosphorylation. Taken together, these results suggest that wogonin (**44**) inhibits the 5-LO/BLT2/ERK/IL-8/MMP-9 signaling cascade. Most importantly, when MDA-MB-231 cells were treated with wogonin (**44**) before LPS stimulation and then intraperitoneally injected in *nude* mice, the number of small bowel metastases was markedly reduced as compared to vehicle and LPS treatment [121].

Silibinin (**8**) was shown to down-regulate MMP-2 expression *via* the JAK2/STAT3 pathway and to inhibit the migration and invasive potential of MDA-MB-231 cells [122]. Moreover, silibinin (**8**) treatment produced a loss of actin stress fiber organization and reduced MMP-9 and paxillin protein expression. The compound also promoted the expression of mitochondrial fusion-associated proteins such as optic atrophy 1 (OPA1) and mitofusin (MFN)-1 and −2, but reduced the expression of dynamin-related protein 1 (DRP1). Silibinin (**8**) affected mitochondrial biogenesis by down-regulating mitochondrial transcription factor A (TFAM), peroxisome proliferator-activated receptor gamma co-activator (PGC1) and nuclear respiratory factor 2 (NRF2). Silibinin (**8**) also decreased ROS levels and the production of oxidized mitochondrial DNA, which resulted in decreased protein levels of nucleotide-binding domain and leucine-rich repeat (NLR) pyrin domain containing 3 (NLRP3), cleaved IL-1β and caspase-1, as well as the inhibition of NLRP3 inflammasome [123].

Apigenin (**2**) also inhibited the migration and invasiveness of MDA-MB-231 cells in a dose-dependent manner, suppressing IL-6 expression

[124,125]. *In vivo*, apigenin (**2**) reduced MDA-MB-231 cell-derived tumor growth in *nude* mice, rendering decreased expression levels of pSTAT3, pERK, PI3K and pAKT proteins in tumor tissues [118]. Luteolin (**4**), but not its glycosides, suppressed TPA-induced MMP-9 mRNA expression at non-cytotoxic concentrations in MDA-MB-231 cells, and inhibited migration and invasion in transwells with TPA-stimulated cells [118]. Luteolin (**4**) was also shown to epigenetically regulate MMP-9 expression *via* AKT/mTOR in BT-20 androgen receptor-positive TNBC cells, reducing the acetylation of histone 3 K27 (H3K27) and K56 (H3K56) and decreasing the binding levels of H3K27ac and H3K56ac on MMP-9 promoter [126].

Myricetin (**45**) reduced migration and invasion in MDA-MB-231Br cells, a cell line derived from MDA-MB-231 which metastasizes to the brain, as observed in wound-healing and transwell assays [127]. Myricetin (**45**) treatment down-regulated MMP-2 and -9 mRNA and protein expression, as well as enzyme activity. Myricetin (**45**) also suppressed the mRNA expression of α(2,6)-sialyltransferase *ST6GALNAC5,* which promotes brain metastasis formation and is considered the key enzyme in α-series ganglioside biosynthesis [128]. Importantly, mice intravenously injected with 4T1 cells and intraperitoneally inoculated with myricetin (**45**) showed a significantly lower number of lung nodules [127]. Formononetin (**46**) also affected the migration and invasion of MDA-MB-231 and 4T1 cells in wound-healing and chamber invasion assays. Furthermore, formononetin (**46**) reduced MMP-2 and -9 and increased tissue inhibitor of metalloproteinase (TIMP)-1 and −2 protein and mRNA expression. In addition, formononetin (**46**) inhibited the phosphorylation of AKT and PI3K. *In vivo*, *nude* mice injected with MDA-MB-231 cells *via* the tail vein and intraperitoneally inoculated with formononetin (**46**) showed a dramatic reduction in lung metastasis and longer survival than those treated with vehicle, as observed in Kaplan-Meier analysis [129]. Recently, formononetin (**46**) was shown to delay migration in MDA-MB-231 and human BT-549 TNBC cells, reduce the expression of lncRNA AFAP1-AS1, CDK4 and RAF-1 serine/threonine kinase, and increase the expression of miR-195 and miR-545, which was postulated to alleviate TNBC malignancy [130].

Baicalein (**47**) inhibited MDA-MB-231 cell adhesion to fibronectin and motility in wound-healing cell migration assays. In this case, flavonoid treatment blocked MDA-MB-231 cell invasion in Matrigel™-coated chambers, as well as the phosphorylation of AKT, ERK, P38 and JNK. Baicalein (**47**) also suppressed the activity and expression of MMP-2 and -9, probably through the MAPK signaling pathway [131]. Proanthocyanidin (**48**) from red rice reduced the expression of extracellular matrix (ECM) degradation-associated proteins, including MMP-9, membrane type-1 matrix metalloproteinase (MT1-MMP), urokinase plasminogen activator (uPA), urokinase plasminogen activator receptor (uPAR) and plasminogen activator-1 (PAI-1), and also reduced collagenase and MMP-9 activity in MDA-MB-231 cells. Furthermore, proanthocyanidin (**48**) significantly suppressed ICAM-1 and IL-6 expression. In cell migration and invasion studies using gelatin-coated and Matrigel™--coated filters, respectively, proanthocyanidin (**48**) favored anti-invasive activity. In addition, proanthocyanidin (**48**) reduced the DNA-binding activity of NF-κB, which usually induces ECM degradation-associated proteins [132]. Similarly, compound **49**, an epigallocatechin gallate (EGCG) derivative (carrying a methyl-carbonate substituent at the 4″ position), showed potent inhibition of PAI-1 and uPA expression in MDA-MB-231 cells; after treatment, a marked attenuation was detected in pERK, pP38 and NF-κB levels. In addition, compound **49** reduced cell migration in wound-healing assays, invasion through vitronectin-coated filters, and MMP-2 and -9 secretion [133].

3.2.3. Reversion of epithelial-mesenchymal transition by flavonoids

Fisetin (**36**) suppressed the growth and metastasis of MDA-MB-231 and BT-549 cells through EMT reversion. Immunofluorescence studies confirmed the up-regulation of E-cadherin, down-regulation of vimentin and remodeling of cytoskeletal protein F-actin in the cytoplasm. Also, EMT reversion involved the suppression of PI3K/AKT/glycogen synthase kinase 3β (GSK-3β) signaling. Moreover, as demonstrated *in vivo* in metastatic breast cancer xenograft models, fisetin (**36**) reduced lung metastasis and modulated the expression of EMT molecules and PTEN/AKT/GSK-3β as in the *in vitro* model [134]. In turn, taxifolin (**50**) also promoted EMT reversion in MDA-MB-231 and 4T1 cells, producing the up-regulation of E-cadherin and claudin and the down-regulation of N-cadherin and vimentin. After treatment, cytoskeletal protein F-actin was depolymerized diffusely in the cytoplasm, and SNAIL and SLUG were down-regulated. Meanwhile, protein and mRNA expressions of β-catenin were dose-dependently down-regulated by taxifolin (**50**), an effect neutralized by β-catenin over-expression by adenoviruses. *In vivo*, taxifolin (**50**) markedly inhibited primary tumor growth and reduced the number of lung metastases in a 4T1 xenograft mouse model [135].

Baicalin (**51**), a flavonoid compound isolated from the roots of *Scutellaria lateriflora* Georgi, did not affect MDA-MB-231 or 4T1 cell viability (10–100 μM) *in vitro* but inhibited EMT [136]. Immunofluorescence studies showed a decrease in vimentin and SLUG in baicalin-treated MDA-MB-231 and 4T1 cells. Furthermore, western blotting and qRT-PCR showed the up-regulation of E-cadherin and claudin, and the down-regulation of N-cadherin, vimentin, SNAIL and SLUG after treatment. In Balb/c mice subcutaneously inoculated with 4T1 cells, baicalin (**51**) treatment decreased vimentin, SLUG and β-catenin expression in primary tumors and reduced the number of lung and liver metastases [136].

Luteolin (**4**) produced E-cadherin and claudin up-regulation and N-cadherin, vimentin, SLUG and β-catenin down-regulation in MDA-MB-231 and BT-549 cells. In *nude* mice subcutaneously injected with MDA-MB-231 cells, luteolin (**4**) reduced the number of lung nodules, an effect counteracted by β-catenin over-expression [137,138]. Likewise, luteolin (**4**) increased E-cadherin and reduced fibronectin, N-cadherin and vimentin in MDA-MB-231 and 4T1 cells. Luteolin (**4**) also inhibited HIPPO pathway transcriptional co-activators YAP and TAZ by promoting proteasome-dependent degradation without affecting their mRNA levels. This compound further decreased the nuclear translocation of YAP/TAZ and the mRNA expression of their target genes in both cell lines and, most importantly, inhibited TAZ-induced EMT. Consistently, luteolin (**4**) treatment inhibited tumor growth in mice xenografted with 4T1 cells and reduced YAP/TAZ expression in tumor sections [139]. In turn, chalcone cardamonin (**52**) significantly increased the expression of E-cadherin but reduced the expression of mesenchymal markers such as SNAIL, SLUG and vimentin in BT-549 cells. Accordingly, in a murine 4T1 breast cancer model in Balb/c mice, cardamonin (**52**) treatment promoted a reduction in tumor volume as compared to untreated animals [140,141].

Apigenin (**2**) also reversed EMT, rendering lower SNAIL and N-cadherin expression levels in MDA-MB-231 cells. In *nude* mice, apigenin (**2**) impaired tumor growth in a xenograft model derived from these TNBC cells; tumor tissues from flavonoid-treated animals showed decreased expression levels of pSTAT3, pAKT and N-cadherin [124]. Moreover, apigenin (**2**) suppressed stemness properties, reducing $CD44^{+}/CD24^{-}$ cancer-stem cell subpopulations and the number of mammospheres in MDA-MB-231 and MDA-MB-436 cells. In addition, apigenin (**2**) decreased YAP/TAZ activity and the expression of their target genes, and disrupted YAP/TAZ/TEAD protein-protein interaction [125].

3.2.4. Anti-angiogenic actions of flavonoids in triple-negative breast cancer

Several flavonoids have shown anti-angiogenic actions on endothelial and TNBC cells [89,142]. For instance, glabridin (**54**) inhibited *in vitro* angiogenesis; MDA-MB-231 cell-conditioned medium caused the formation of capillary-like structures in HUVEC cells, a phenomenon blocked by glabridin (**54**). In addition, this flavonoid prevented HUVEC and MDA-MB-231 cell migration, which was associated with an increase in $\alpha_v\beta_3$ integrin proteosome degradation. Glabridin (**54**) decreased the phosphorylation of focal adhesion kinase (FAK) (at Tyr 397, 576 and 925) in MDA-MB-231 and HUVEC cells and reduced SRC active form (with Tyr 416 phosphorylation), thus increasing its inactive form (with Tyr 527 phosphorylation). Glabridin (**54**) also blocked AKT and ERK1/2

activation. In angiogenesis assays where MDA-MB-231 cells were mixed with Matrigel™ and injected into *nude* mice, glabridin (**54**) reduced the formation of functional blood vessels within Matrigel plugs. Also, hemoglobin levels in the plugs containing TNBC cells were 1.5-fold higher than in those containing only Matrigel™, an effect offset by glabridin (**54**) [143].

Chalcone isoliquiritigenin (**55**), a natural flavonoid isolated from the root of *Glycyrrhiza glabra* [144], was shown to inhibit angiogenesis *in vitro*, inhibiting HUVEC cell proliferation in response to VEGF. Similarly, isoliquiritigenin (**55**) blocked VEGF-induced tube formation, invasion and migration in HUVEC cells, suppressing VEGFR2 signaling. In MDA-MB-231 cells, isoliquiritigenin (**55**) blocked VEGF expression by promoting HIF-1α proteasome degradation. *In vivo,* isoliquiritigenin (**55**) intraperitoneally injected in *nude* mice previously inoculated with MDA-MB-231 cells inhibited tumor VEGF, pVEGFR2 and MMP-2 expression and reduced tumor microvessel density [145].

Wogonoside (**26**) has been shown to effectively inhibit angiogenesis in TNBC. Indeed, wogonoside (**26**) blocked VEGF expression in MDA-MB-231 cell-derived tumors *in vivo* and suppressed VEGF secretion, VEGF mRNA expression and VEGF promoter activity *in vitro* in both MDA-MB-231 and MDA-MB-468 cells. Wogonoside (**26**) also affected Hedgehog signaling, which is increased in TNBC cells and regulates the *VEGFA* gene. This flavonoid inhibited glioma-associated oncogene homolog protein 1 (GLI1) nuclear translocation and transcriptional activity and promoted ubiquitination-dependent degradation of transmembrane receptor Smoothened (SMO), an upstream GLI1 activator. In tubulogenesis assays, HUVEC incubated with TNBC cell-conditioned medium showed inhibition of tube-like structures by wogonoside (**26**). Accordingly, in Matrigel™-plug assays in *nude* mice, wogonoside (**26**) suppressed blood vessel formation for both MDA-MB-231 and MDA-MB-468 cells [146].

A synthesized flavonoid with a piperazine substitution, compound **56** (named LYG-202 by the authors) [147], reduced the number of tube-like structures produced by EA.hy 926 endothelial cells previously treated with MDA-MB-231 cell-conditioned medium under hypoxia. In plug assays *in vivo*, Matrigel™ mixed with MDA-MB-231 cells promoted greater blood vessel formation than Matrigel™ alone, an angiogenic event inhibited by compound **56**. In transwell assays, MDA-MB-231 cells in the lower chamber strongly stimulated EA.hy 926 cell migration and invasion from the upper chamber under hypoxia, while compound **56** treatment reduced EA.hy 926 cell migration and invasion rates. Accordingly, after compound **56** treatment, F-actin became less prominent in EA.hy 926 cells, with cytoplasmic stress fiber reduction. The secretion of chemokine C-X-C motif chemokine 12 (CXCL12) and expression of C-X-C chemokine receptor type 7 (CXCR7) were also reduced, which led to the suppression of ERK/AKT/NF-κB signaling in endothelial cells [148].

Myricetin (**45**) was demonstrated to inhibit angiogenesis in TNBC [149] and endothelial cells [150]. This flavonoid suppressed tumor growth in 4T1 cell-derived xenografts and reduced microvascular density, as determined through CD31 immunohistological staining. VEGF content in the serum of tumor-bearing mice and in the conditioned media from 4T1 cells was also reduced by myricetin (**45**). Moreover, this compound reduced blood vessel density in chick embryo chorioallantoic membrane and yolk sac membrane angiogenesis assays, and inhibited microvascular formation in rat aortic ring assays. Myricetin (**45**) further reduced HUVEC cell migration with no impact on endothelial cell proliferation, reducing VEGFR2, pP38 and P38 protein expression levels upon co-treatment with VEGF in HUVEC cells. In conclusion, myricetin (**45**) reduced VEGF protein levels *in vivo* and *in vitro*, affecting the activation of P38/MAPK pathway by VEGF [149].

4. Advantages, disadvantages and current challenges of flavonoids for breast cancer therapy

Resistance towards radiotherapy, endocrine therapy, chemotherapy and/or immunotherapy remains the leading cause of breast cancer-related mortality, and targeted therapy requires the development of new compounds. Some flavonoids are promising bioactive compounds able to modulate key signaling pathways that might mitigate drug resistance to current antineoplastic therapies. Cytotoxic and anti-angiogenic effects were often promoted while cell invasion mediated by MMP-2/-9, TGF-β and β-catenin pathways as well as PI3Kγ signaling were frequently impeded by diverse simple and common flavonoids. Fig. 3 depicts the main signaling pathways discussed in this overview and describes several mechanistic effects produced by simple natural and synthetic flavonoids. Of note, cytotoxic effects on luminal and TNBC cells caused by several of these flavonoids converge in: i) cell-cycle arrest, with down-regulation of cyclins D1 and B1, CDKs or CHK1/2; ii) the intrinsic apoptotic pathway, causing increased BAX, decreased BCL-2, release of cytochrome *c* to extra-mitochondrial compartments and a decline in mitochondrial membrane potential; iii) the extrinsic apoptotic pathway with caspase-8 activation, which subsequently induces caspase-3 activity. Other mechanisms in luminal breast cancer cells such as ERα signaling pathway associated with IGF-1R, with reduced phosphorylation of IRS-1, AKT, ERK1/2 are commonly affecting proliferation upon flavonoid treatment.

Outstanding targets of some flavonoids might support their potential future applications in cancer therapy; for example, a probable function as PARP inhibitor in TNBC has been proposed for luteolin (**4**) [119]. Although PARP inhibitors such as olaparib, niraparib and talazoparib have been tested in clinical trials in metastatic breast cancer patients with BRCA1/2 mutations [151], objective response rates have only been partially successful [152]. Therefore, new PARP inhibitors are needed to improve overall patient survival and selected flavonoids and their precise derivatives might offer that advantage.

Although various evidences seem to show flavonoid anti-tumor effects in luminal and triple-negative breast cancer cells, several crucial concerns attract our attention. One general concern is related to high flavonoid doses required for certain compounds in order to produce a defined function, which is a disadvantage for *in vivo* treatments because of toxicity. In this sense, some *in vitro* experiments compilated in this revision have employed flavonoid concentrations higher than the IC_{50} of the corresponding compound, which should be avoided because it might reflect secondary events after cell cycle arrest or apoptosis.

Another concern about certain flavonoids is their chemical similarity to E2. Some flavonoids can modulate ERα or ERβ as agonist or antagonists acting as phytoestrogens, which implies a double-edged sword for breast cancer treatment [153]. In luminal breast cancer, ERα and ERβ are expressed in a given ratio, and the role of ERβ isoforms remains controversial. In TNBC, ERβ and its different isoforms are expressed (but not ERα) and some of them might be related to tumor progression [154]. In fact, most phytoestrogens are less potent estrogens than E2 [153]. In particular, apigenin (**2**) and kaempferol (**9**) were classified as weak ERα agonists that activate ERα [155], while genistein (**33**) can bind to both α and β subtypes of ERs, showing increased affinity for ERβ, which usually counteracts the proliferative activity of ERα in luminal breast cancer (*i.e.* ERβ1) [156]. Important criteria for the binding affinity to ERα were reported for certain flavonoids, which might include: i) the presence of an aromatic ring with an OH group, to mimic the E2 A ring with its 3-OH group and thus allow the formation of a hydrogen bond with amino acid Glu^{353}, Arg^{394} and a water molecule in the ER ligand binding domain; ii) a ligand with a second OH group, to favor an additional hydrogen bond to mimic E2 17β-OH and form a hydrogen bond with His^{524} in the ER ligand binding domain; this hydrogen bond is optimal when the distance between the two oxygens on the opposite sides of the molecule is similar to those in E2 [157]. Therefore, further studies on certain flavonoids as ERα or ERβ modulators is deemed essential for breast cancer and should include the use of global and targeted gene expression in wild-type and ERα/β -null breast cancer cells, transactivation assays, cell-free ERα/β co-regulator interaction assays, improved docking studies and animal models. To summarize, ERα/β agonist or antagonist role for a given flavonoid might be an obstacle or a benefit depending on breast tumor marker expression and should be

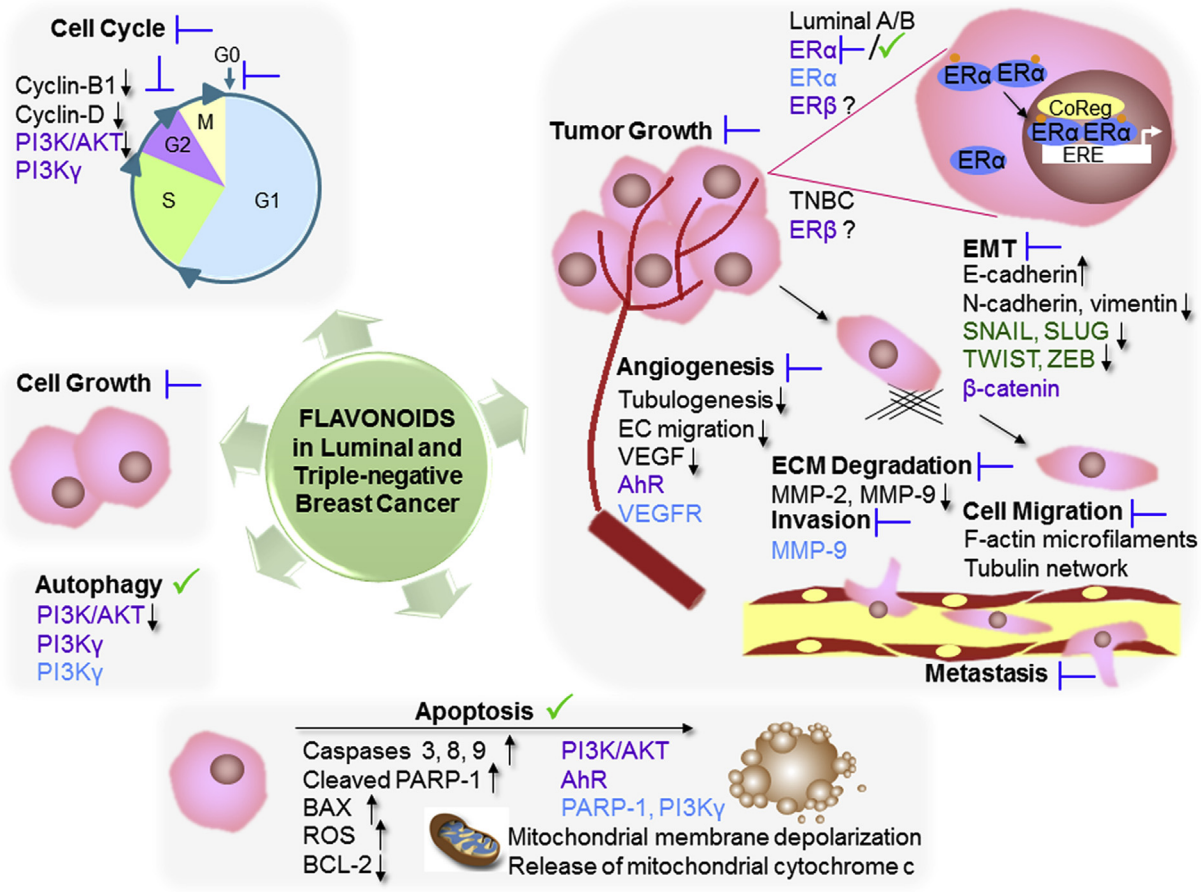

Fig. 3. Mechanisms of action frequently exerted by flavonoids in luminal and triple-negative breast cancer. Flavonoids produce numerous biological effects on breast tumor cells, modulating different signaling pathways. Certain flavonoids affect proliferation *via* cell cycle arrest, trigger apoptosis pathways, generate reactive oxygen species and induce autophagy modulating PI3Kγ signaling, which finally causes a reduction in tumor volume. Also, flavonoids can induce down-regulation of mesenchymal markers (and up-regulation of epithelial markers) *via* epithelial-mesenchymal transition-related transcription factors and the β-catenin pathway. In addition, tumor cell migration, invasion and angiogenic processes are inhibited through the modulation of metalloproteases, cytoskeletal regulation, vascular endothelial growth factor and aryl hydrocarbon receptor signaling. Some biological processes are inhibited (⊣) whereas others are induced (✓) by flavonoids. Signaling pathways involved are highlighted in violet, transcription factors are highlighted in green, and potential targets of certain flavonoids in sky blue. Some flavonoids might act as phytoestrogens and even might show biphasic effects on estrogen receptor α and β. EC: endothelial cell. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

carefully evaluated in luminal and TNBC patients.

An additional disadvantage of flavonoids is their low water solubility and poor absorption, resulting in numerous *in vivo* and *in vitro* studies trying to encapsulate them in nanocarriers for anti-cancer drug delivery and thus bypass their hydrophobicity [158]. For example, EGCG- [159,160] or fisetin-loaded [161,162] nanoparticles and their inhibitory effects on breast cancer cells have been well-documented. Interestingly, co-encapsulation of TAM and quercetin (3) in polymeric nanoparticles has demonstrated anti-tumor efficacy with anti-angiogenic effects [163]. Of note, silibinin (8) encapsulated in aminoethyl anisamide-polyethylene glycol-polycaprolactone nanoparticles and intravenously delivered produced better tumor inhibition effects in mice carrying 4T1 breast cancer cell-derived tumors than non-encapsulated silibinin (8); indeed, encapsulated silibinin (8) induced a reduction in regulatory T (Treg) and MDSC cells, suppressed angiogenesis and inhibited collagen formation in tumor tissues [164]. Thus, the translational perspectives of flavonoid nanostrategies [165] in breast cancer are encouraging and may lead to the development of novel delivery systems for combinatorial therapy including flavonoids to reduce chemoresistance.

One decisive worry is the very scarce evidence from anti-cancer clinical trials with flavonoids. In fact, effects of flavonoids, mostly tested in preclinical breast cancer models, should be translated into clinical cancer treatment research, where there are still really few records (Table 4). New randomized trials *versus* placebo are needed to test the feasibility of certain flavonoids as an adjuvant therapy mainly after surgical resection of primary breast tumor or in the advanced metastatic setting.

In summary, future challenges focus on: i) novel computational methods are needed to predict flavonoid modulation of molecular targets such as ERα/β and their dose-response characteristics, which can be linked to Adverse Outcome Pathway (AOP) frameworks; ii) new targeted nanosystems must be designed to improve bioavailability and/or reduced toxicity of flavonoids and co-delivered drugs; and iii) additional studies are required on intracellular and/or extracellular metabolites potentially produced from each flavonoid *in vivo* [33,166]. Finally, one outstanding question still remains to be solved: Why are clinical trials with flavonoids so scarce for breast cancer treatment? Further basic and clinical research will hopefully unravel challenges and precisely define therapeutic relevance of certain flavonoids in luminal and triple-negative breast cancer.

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Authors' contributions

V.S.V., M.M., M.F.T. and M.T.E. designed and conducted the review, performed literature search, wrote the manuscript and produced illustrations and tables. Moreover, M.M. structurally classified each compound. All authors contributed to manuscript revision and approved the submitted version.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AhR	aryl hydrocarbon receptor
AIF	apoptosis-inducing factor
AOP	adverse outcome pathway
APC	axin/adenomatous polyposis coli
ASK1	apoptosis stimulating kinase 1
ATF4	activating transcription factor 4
ATG5	autophagy-related gene 5
BATF	basic leucine zipper ATF-like transcription factor
BAK1	BCL-2 antagonist/killer 1
BAX	BCL-2 associated X
BCL-2	B-cell lymphoma 2
BCL2L11	Bcl-2-like 11
BCL-XL	B-cell lymphoma-extra large
BLT2	leukotriene B4 receptor 2
BRCA-1	breast cancer type 1
CCND1	cyclin D1
CCR7	C–C chemokine receptor type 7
CD	cluster of differentiation
CDC2	cell division control protein 2 homolog
CDKs	cyclin-dependent kinases
CIDEA	cell death-inducing DNA fragmentation factor alpha subunit-like effector A
CXCL12	chemokine C-X-C motif chemokine 12
CXCR-4	C-X-C chemokine receptor type 4
CXCR7	C-X-C chemokine receptor type 7
CYP1	cytochrome P450 family 1
CHK1/2	checkpoint kinase-1/-2
DRP1	dynamin-related protein 1
DVL	dishevelled
E2	17β-estradiol
ECM	extracellular matrix
EGCG	epigallocatechin gallate
EMT	epithelial-mesenchymal transition
ER	estrogen receptor
FAK	focal adhesion kinase
FAS (CD95)	Fas antigen
FOXP3	forkhead box P3
FOXM1	forkhead box M1
GLI1	glioma-associated oncogene homolog protein 1
GRP78	glucose-regulated protein with a molecular mass of 78
GSK-3β	glycogen synthase kinase
HER2	human epidermal growth factor receptor 2
HIF1α	hypoxia inducible factor 1 subunit alpha
HUVEC	human umbilical vein endothelial cell
ICAM-1	intercellular adhesion molecule-1
IC_{50}	half-maximal inhibitory concentration
IGF-1	insulin-like growth factor 1
IGF-1R	insulin-like growth factor 1 receptor
IκBα	NF-κB inhibitor α
IL	interleukin
IRS-1	insulin receptor substrate-1
Ki67	Ki-67 antigen
LATS1	large tumor suppressor kinase 1
LC3	microtubule-associated protein light chain 3
LDH	lactate dehydrogenase
LEF/TCF	lymphoid enhancer factor/T-cell factor
Lnc	long non-coding
5-LO	5-lipoxygenase
LPS	lipopolysaccharide
MAML1	mastermind-like-1
MEK	mitogen-activated protein kinase kinase
MAPK	mitogen-activated protein kinase
2ME2	2-methoxyestradiol
miRNA	microRNA
MFN	mitofusin
MMP	metalloproteinase
MPA	medroxyprogesterone acetate
MST1/2	mammalian STe20-like 1 and 2
MT1-MMP	membrane type-1 matrix metalloproteinase
MTT	3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide
nDELs	natural products enriched DNA-encoded chemical libraries
NFAT	nuclear factor of activated T cell
NICD	intracellular domain of NOTCH
NLRP3	nucleotide binding domain and leucine-rich repeat (NLR) pyrin domain containing 3
NRF2	nuclear respiratory factor
OCT	octamer-binding transcription factor
OPA1	optic atrophy 1
PAI-1	plasminogen activator-1
PARP	poly (ADP-ribose) polymerase
PCNA	proliferating cell nuclear antigen
PD-L1	programmed cell death 1 ligand 1
PGC1	peroxisome proliferator-activated receptor gamma coactivator
PHB2	prohibitin 2
PI	propidium iodide
PLK1	polo-like kinase 1
PR	progesterone receptor
RAF-1	raf-1 proto-oncogene serine/threonine kinase
RLIP76	ral-interacting protein 76
ROS	reactive oxygen species
SERM	selective estrogen receptor modulators
siRNA	small interfering RNA
SMAD	mothers against decapentaplegic homolog
SMO	smoothened
SPR	surface plasmon resonance
ST6GALNAC5	st6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 5
SRC	protooncogene Rous sarcoma
TAM	tamoxifen
TAZ	transcriptional co-activator with a PDZ-binding domain
TEAD	TEA domain transcription factor 1
TFAM	mitochondrial transcription factor A
TFF1	trefoil factor 1
TGF-β	transforming growth factor-β
TIMP	tissue inhibitor of metalloproteinase
TNBC	triple-negative breast cancer
TNFα	tumor necrosis factor α
TPA	12-O-tetradecanoylphorbol-13-acetate
TRX-1	thioredoxin

uPA	urokinase plasminogen activator
uPAR	urokinase plasminogen activator receptor
VCAM-1	vascular cell adhesion protein 1
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
vWF	von Willebrand factor
WNT	wingless-type MMTV integration site family
XRE	xenobiotic response element
YAP	yes-associated protein
ZO-1	zonula occludens-1

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