



Luteolin: Anti-breast Cancer Effects and Mechanisms

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Abstract

Luteolin is a flavonoid compound and exhibits antioxidant, antiinflammatory, antibacterial, antidiabetic and antiproliferative properties. Studies have shown that luteolin may inhibit cell proliferation, metastasis, and angiogenesis of numerous types of cancers, including breast cancer, through inducing cell cycle arrest and apoptosis and by modulating cell signaling. In this review, we have summarized the recent studies on inhibitory effects and underlying mechanisms of luteolin in breast cancer. These studies support that luteolin is a promising drug to treat breast cancer.

Introduction

Luteolin is the nickname of 3', 4', 5, 7-tetrahydroxyflavone. It belongs to biologically active flavonoids that are widely found in the plant kingdom.¹ Dietary intake of flavonoids is inversely associated with risk of lung, prostate, stomach and breast cancers in humans.²⁻⁴ Luteolin contains three rings in its molecule, including two benzene rings (A, B) and an oxygen-containing (C) ring, which is called the C6-C3-C6 structure (Fig. 1). There is a C2-3 double bond in the oxygen-containing (C) ring, and two hydroxyl groups in each benzene ring.⁵ Luteolin does not have an -OH substitution on C3.⁶ The C2-3 double bond and C3' and C4' hydroxyl groups of luteolin are essential for its biochemical and biological activities,⁷ including antioxidant, antiinflammatory, antibacterial, antidiabetic and antiproliferative actions.^{8,9} In the past decades, the anticancer effect of luteolin has been demonstrated on many kinds of cancers, such as hepatocellular carcinoma, melanoma, and gastric carcinoma, ovarian cancer, colorectal cancer, and breast cancers.¹⁰⁻²²

Breast cancer is the most common and life-threatening cancer diagnosed among women worldwide.²³ According to genomic expression profiles and immunohistochemical staining of a few

molecular markers, such as estrogen receptor (ER), PR, Her2, and Ki67, breast cancer is classified into the following five subtypes: luminal A (ER/PR⁺HER2⁻Ki-67^{low}), luminal B (ER/PR⁺HER2⁻Ki-67^{high}), Her-2-enriched (ER/PR⁻HER2⁺Ki-67^{high}), triple negative/basal-like (ER/PR⁻HER2⁻Ki-67^{high}), and "other" (including all those that cannot be attributed to the four subtypes). This molecular classification predicts cancer progression and directs the choice of therapeutic modality.²⁴⁻²⁹

Patients with high expression of HER-2 and Ki-67 were found to have a poor prognosis.^{30,31} The luminal A subtype is more responsive to endocrine therapy than other subtypes. The luminal B subtype can be treated by chemotherapy. The Her-2-enriched subtype is treated by HER-2-targeted therapy, and anthracycline-based chemotherapy. The triple negative/basal-like subtype is treated by platinum-based chemotherapy and PARP inhibitors.²⁴⁻²⁹

Although therapeutic approaches for breast cancer have been developed, the cure of breast cancer is still unsatisfactory because of the heterogeneity and recalcitrant nature towards various drug therapies.^{24-29,32} To control proliferation and metastasis during breast cancer therapy, novel drugs are needed. In this paper, we have summarized the studies on the anticancer effects of luteolin on breast cancer.

Anticancer effects of luteolin on breast cancer

The anticancer effects of luteolin on breast cancer have been investigated using pertinent cell lines which are relevant to molecular subtypes of breast cancer.³³ Luteolin was shown to effectively block the IGF-1-stimulated luminal A subtype ER α -positive MCF-7 cell proliferation in a dose- and time-dependent manner³⁴ and to suppress triple negative/basal-like ER α -negative MDA-MB-231 cell growth.³⁵ Luteolin was also shown to decrease the viability of breast cancer cells MCF7/6 and MDA-MB231-1833.³⁶ Luteolin-supplementation at 0.01% or 0.05% significantly reduced tumor burden in nude mice inoculated with MDA-MB-231 cells.³⁵ This was confirmed by studies that showed dose-dependent inhibitory effects of luteolin on the proliferation of MCF-7 cells and MDA-MB-231 cells.^{37,38}

Extensive studies have shown that luteolin significantly inhibits cell cycle of MCF-7 and MDA-MB-231 cells, resulting in cell cy-

Keywords: Luteolin; Breast Cancer; Mechanisms; Inhibitory Effects.

Abbreviations: AEG-1, astrocyte elevated gene 1; AKT, protein kinase B; AP-1, activator protein-1; CAT, catalase; DR5, death receptor 5; EGFR/HER, epidermal growth factor receptor; EMT, epithelial mesenchymal transition; ER, estrogen Receptor; ERK, extracellular signal-regulated kinase; ESP, estrogen signaling pathway; FAS, fatty acid synthase; JNK, Jun N-terminal kinase; KDR, vascular endothelial growth factor receptor 2; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; NF- κ B, nuclear factor-kappa B; PARP, poly ADP-ribose polymerase; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; PLK-1, polo-like kinase 1; PR, progesterone receptor; ROS, reactive oxygen species; SOD, superoxide dismutase; STAT, signal transducers and activators of transcription; TNBC, triple-negative breast cancer; TNF α , tumor necrosis factor alpha; TPL2, tumor progression locus 2; VEGF, vascular endothelial growth factor; VRK1, vaccinia-related kinase 1.

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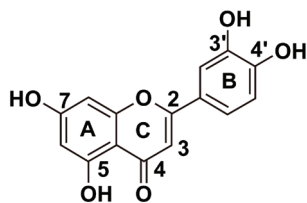


Fig. 1. Luteolin molecular structure. The C2-3 double bond and C3' and C4' hydroxyl groups of luteolin are essential for the biochemical and biological activities.

cle arrest at the G2/M and S stages.^{34,38–40} Luteolin can also induce apoptosis in breast cancer cells.^{34–36} These studies support that luteolin inhibits the proliferation of breast cancer cells of various subtypes. In an epidemiological study on dietary intake of selected flavonols, flavones and flavonoids, luteolin in food was shown to have no anticancer effect.⁴¹ This might be due to low daily uptake of luteolin (<2.0 mg/d). The therapeutic doses or concentration of luteolin are much higher and could be 10–30 mg/mL according to the experimental research findings.

The formation of new blood vessels from the preexisting vasculature (angiogenesis) is a crucial stage in cancer progression. Indeed, studies showed that luteolin exerted strong antiangiogenesis activity in chick chorioallantoic membrane.^{38,42} Metastases are the primary cause of human cancer deaths. Most breast cancer-related deaths from triple negative breast cancer (TNBC) occur following metastasis of cancer cells and development of tumors at secondary sites. Because TNBCs lack the three receptors (ER, PR, and HER2) targeted by current chemotherapeutic regimens, they are typically treated with extremely aggressive and highly toxic non-targeted treatment strategies.

Luteolin can efficiently suppress migration and invasion of the highly metastatic TNBC cell lines MDA-MB-231 and BT-549, and inhibit the lung metastases of breast cancer xenograft tumors derived from MDA-MB-231 cells.^{38,42–44} Luteolin can also significantly inhibit migration of ER α -positive MCF-7,³⁸ inhibit cell migration and viability of human MDA-MB-435 and MDA-MB-231 (4175) LM2 TNBC cells *in vitro*, and suppress metastasis of these cells to the lungs in a mouse metastasis model.⁴⁴ Luteolin may inhibit breast cancer intravasation through the lymphatic barrier, as revealed by an *in vitro* assay that showed luteolin exerted an anti-intravasative effect of MDA-MB231 breast cancer spheroids through the lymph endothelial barrier.⁴⁵ Luteolin can efficiently suppress the migration and invasion of MDA-MB-231 and MCF-7 cells as well.^{38,42–45} Epithelial mesenchymal transition (EMT) is also a key event in metastasis. Luteolin can reverse EMT of MDA-MB-231 and BT-549 breast cancer cells, which may be mediated by down-regulation of β -catenin.⁴³

All these studies support that luteolin may induce cell cycle arrest at the G2/M and S stages, as well as apoptosis, and inhibit migration and epithelial mesenchymal trans-differentiation of breast cancer cells, thereby inhibiting the development, progression and metastasis of breast cancer.

Mechanism involved in anticancer effects of luteolin on breast cancer

Apoptotic pathways

Luteolin-induced apoptosis involves reactive oxygen species (ROS)

generation, DNA damage, activation of the ATR \rightarrow Chk2 \rightarrow p53 signaling pathway, inhibition of the nuclear factor (NF)- κ B signaling pathway, activation of the p38 pathway and depletion of antiapoptotic proteins.⁴⁶ In MCF-7 cells, luteolin enhanced the expression of death receptors, such as DR5, and enhanced the activities of caspase-8 and -9, which in turn induced caspase-3 activity in a dose-dependent manner, followed by inactivation of PARP. Luteolin also induced mitochondrial membrane potential collapse and cytochrome c release, and increased Bax expression by inhibiting expression of Bcl-2. Therefore, luteolin induces apoptosis by activating the extrinsic and intrinsic pathways.⁴⁷

PI3K/Akt

Luteolin markedly decreases IGF-1-dependent IGF-1R and Akt phosphorylation without affecting extracellular signal-regulated kinase (ERK)1/2 phosphorylation in MCF-7 cells, and the inhibiting IGF-1-mediated PI3K-Akt pathway is dependent on ER α expression, resulting in suppression of MCF-7 cells.³⁴ Luteolin induces cell cycle arrest and apoptosis in breast cancer cells through inhibition of PI3K/Akt activation and increase of FOXO3a activation.⁴⁰ Inhibiting the PI3K/Akt signaling pathways also mediated suppression of the epidermal growth factor receptor (EGFR) signaling pathway and the proliferation of ER α -positive MCF-7 cells and ER α -negative MDA-MB-231 cells by luteolin in a dose-dependent manner.³⁷

EGFR

EGFRs/HERs are implicated in pathogenesis of breast cancer and their over-expression is associated with poorer prognosis and outcomes of breast cancer.^{48–50} Luteolin was shown to down-regulate EGFR expression and inhibit EGF-induced mitogen-activated protein kinase (MAPK) activation in a dose-dependent manner, including the phosphorylation of ERK, p38 and AKT, and to suppress the proliferation of MDA-MB-231 ER-negative breast cancer cells and ER α -positive MCF-7 cells.^{35,37}

Polo-like kinase 1 (PLK-1)

PLK-1 is a mitotic kinase and actively regulates the G2/M transition, mitosis, mitotic exit, and cytokinesis.⁵¹ The over-expression of PLK-1 is strongly correlated with a wide spectrum of human cancers and their poor prognosis.⁵² Luteolin inhibits PLK1 gene expression in MCF-7 breast cancer cells⁵³ and MDA-MB-231 ER-negative breast cancer cells.³⁵ This inhibition is probably caused by decreased acetylation of histone H4 associated with the PLK1 gene promoter.⁵³

Estrogen signaling

It has been shown that luteolin possesses estrogen agonist activity.⁵⁴ However, luteolin exerts its antiestrogen activity by regulating many estrogen signaling pathway (ESP) genes, including GTF2H2, NCOR1, TAF9, NRAS, NRIP1, POLR2A, DDX5 and NCOA3, in MCF-7 breast cancer cells probably through epigenetic mechanism.⁵³ Some breast cancer subtypes, such as luminal A, are considered to be primarily regulated by ESPs, and hormone therapy using antiestrogen drugs, such as tamoxifen, is effective for breast cancers expressing ER α .^{55–57} Therefore, luteolin could

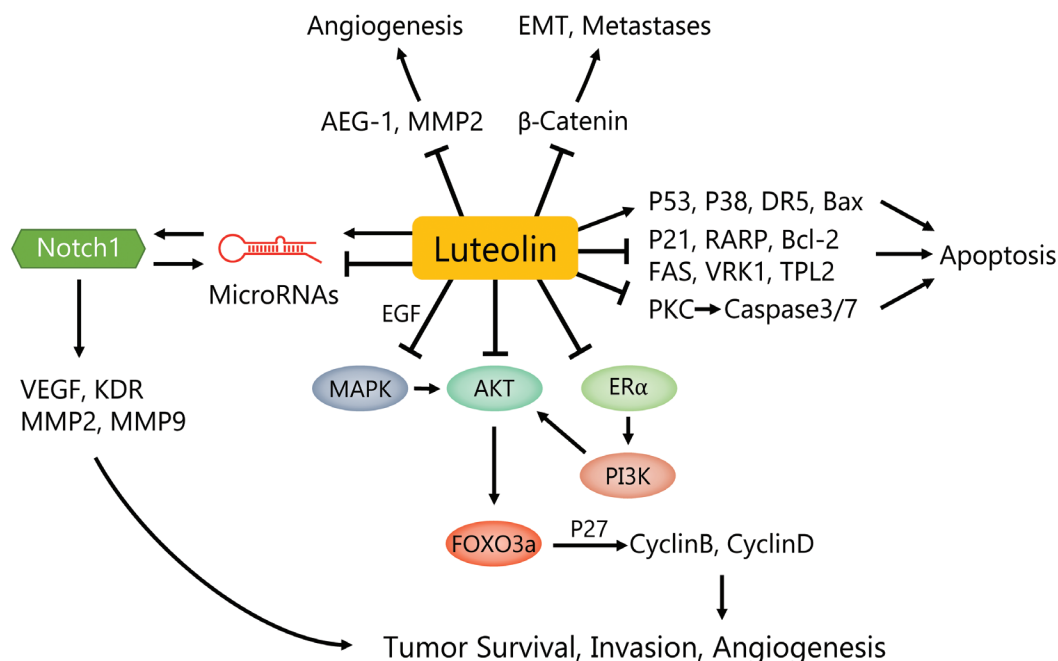


Fig. 2. Luteolin modulates the signaling pathways and inhibits the growth and migration as well as promotes apoptosis of breast cancer cells.

be an effective drug for breast cancer therapy.

Notch and microRNA

Luteolin inhibits Notch signaling and regulates miRNAs. Treatment of MCF-7 and MDA-MB-231 cells with luteolin results in decreasing expression levels of Notch-1, Hes-1, Hey-1, Hey-2 as well as vascular endothelial growth factor (VEGF), cyclin D1 and matrix metalloproteinase (MMP) expression in breast cancer cells. Luteolin induces miR-181a, miR-139-5p, miR-224 and miR-246 expression levels and decreases the miR-155 level in both MCF-7 and MDA-MB-231 cells, and increases miR-34a level in MDA-MB-231 cells. MiR-34a and miR-224 regulates Notch signaling and inhibits breast cancer cell survival migration and angiogenesis.³⁸

Inflammation-related signaling

Luteolin down-regulates the transactivity of NF- κ B and activator protein-1 (AP-1), resulting in inhibition of TNF α -induced COX-2 expression. Luteolin also inhibits TNF α -induced phosphorylation of MAPK/ERK kinase 1/ERK/p90RSK, MAPK kinase 4/Jun N-terminal kinase (c-JNK)/c-Jun, and Akt/p70S6K. These effects of luteolin are probably due to blocking tumor progression via locus 2 serine/threonine kinase (TPL2).⁵⁸

Metastasis-associated signaling

Luteolin down-regulates the expression of astrocyte elevated gene 1 (AEG-1), a novel oncoprotein, and MMP-2.⁴² Relatively low levels of luteolin significantly inhibit VEGF secretion in MDA-MB-231 (4175) LM2 cells, suggesting that it has the ability to suppress a potent angiogenic and cell survival factor.⁴⁴ Luteolin

suppresses the metastasis of TNBC by reversing EMT via down-regulation of beta-catenin expression.⁴³

Luteolin directly inhibits kinases protein kinase C (PKC), VRK1 and TPL2 in breast cancer cells

As reported as early as 1989, luteolin is a PKC inhibitor. It competitively blocks the ATP binding site on the catalytic unit of PKC.⁵⁹ TPL2 is a protooncogene that is over-expressed in various cancer types, including breast cancer.⁶⁰ Luteolin may directly bind TPL2 and inhibit TPL2 activity in an ATP-competitive manner,⁵⁸ leading to similar effects of luteolin on TNF- α -mediated signaling pathways and COX-2 expression.⁵⁸ Recently, luteolin was found to significantly and directly interact with the catalytic domain of vaccinia-related kinase 1 (VRK1), a mitotic kinase that functions in cell cycle regulation, and to reduce VRK1-mediated phosphorylation of the cell cycle-related substrates BAF and histone H3.⁶¹ Therefore, luteolin is a direct inhibitor for kinases such as PKC, VRK1, and TPL2.

Luteolin inhibits fatty acid synthase in breast cancer cells

Luteolin inhibits fatty acid synthase (FAS), which is a key lipogenic enzyme over-expressed in many human cancers, resulting in inhibition of cell growth and induction of apoptosis of prostate and breast cancer cells.^{39,62} Although the underlying mechanism of FAS inhibition by luteolin is not completely clear, the presence of a C-2,3 double bond, a 4-ketone function and hydroxyl groups on positions 5, 7, 3', and 4' plays a favorable role to inhibit lipid synthesis in intact cells.³⁹

Overall, luteolin may modulate multiple cell signaling pathways and target genes in breast cancer cells. These altered pathways lead to cell cycle arrest, apoptosis, and inhibition of cell growth, migration, and epithelial mesenchymal trans-differentiation (Fig. 2).

Luteolin affects the effects of therapeutic drugs on breast cancer

Luteolin enhances the effects of therapeutic drugs on breast cancer

Several studies have provided evidence that luteolin can be used as a chemosensitizer for antitumor agents.^{63–68} Luteolin administered at doses less than 100 μM reverses tumor resistance of 4T1 and MCF-7 cells to doxorubicin and promotes death of tumor cells under hypoxia *in vitro*, although it has only slight effect on cell growth and cytotoxicity of doxorubicin under normoxia. The same was found in 4T1 and MCF-7 bearing mice.⁶⁴ In these models, luteolin suppressed glycolytic flux but did not affect glucose uptake, the P-glycoprotein, antioxidative enzymes under hypoxia *in vitro*, or the intratumor doxorubicin level *in vivo* associated with increased and decreased activity of SOD and CAT in serum and in tumor, respectively.⁶⁴ The combination of celecoxib and luteolin induced synergistic and inhibitory effects on the growth of cancer cells *in vivo* via Akt inactivation and ERK signaling inhibition in MCF-7 and MCF7/HER18 cells and via Akt inactivation and ERK signaling activation in MDA-MB-231 and SkBr3 cells.^{65,66}

Luteolin reduces drug-resistance of human breast cancer cells to tamoxifen via the inhibition of cyclin E2 expression.⁶⁹ Luteolin enhances paclitaxel-induced apoptosis in human breast cancer MDA-MB-231 cells by blocking STAT3.⁷⁰ These studies suggested that luteolin may enhance the effect of chemotherapeutic drugs on breast cancer by reducing drug resistance and promoting apoptotic effects and inhibition of breast cancer cell growth.

Low doses of luteolin protect breast cancer cells from cytotoxicity of therapeutic drugs

In a study by Sato *et al.*⁷¹ luteolin was found to have biphasic effects on viability of the human breast cancer cell line MCF-7. Luteolin at low concentrations, as low as 10 μM , was shown to protect the MCF-7 cells from doxorubicin toxicity, while in contrast, it inhibited cell viability at higher concentrations ($>30 \mu\text{M}$). Luteolin at 10 μM also attenuated doxorubicin-induced cytotoxicity in the presence of the ER antagonist ICI 182 780 and in the MDA-MB-453 human breast cancer cell line. Luteolin reduced doxorubicin-induced ROS generation and increased the antiapoptotic protein Bcl-2 levels in MCF-7 cells treated with doxorubicin. This may contribute to the ameliorating effects of luteolin on doxorubicin-induced cytotoxicity of MCF-7 cells.⁷¹ Therefore, the dosage of luteolin is a critical factor for determining its effects on breast cancer.

Current challenges and future research directions

Breast cancer is a complex disease with a large degree of inter- and intratumoral heterogeneity and personalized therapy should be assumed for cure.^{72–74} Although ER, PR, HER-2 and Ki-67 have been used for molecular classification of breast cancer and have achieved good outcomes, numerous subtypes of breast cancer have been identified based on novel molecular biomarkers,⁷⁵ this surely will lead to better understanding and cure of breast cancer in the future. On the other hand, the corresponding therapeutic drugs should also be developed.

The inhibitory effects and underlying mechanisms of luteolin

on breast cancer can be investigated when combined with traditional endocrine therapy, chemotherapy, and/or targeted therapy for the current and new molecular subtypes. The efficacy of luteolin in clinical treatment of breast cancer remains to be determined. It is also worthy of investigating whether luteolin is useful in male breast cancer and functional in novel personalized therapeutic approaches such as genomics-based therapies and immunity-based therapies.^{76–78}

Conclusion

Luteolin is active in inhibiting the proliferation, progression and metastasis of breast cancer in a dose-dependent manner through suppressing cell cycles, inducing apoptosis, and inhibiting migration and EMT of breast cancer cells. These effects of luteolin are achieved through multiple signaling pathways, such as Notch, PI3K/Akt, MAPK/ERK1/2, EGFR, and NF- κ B (Fig. 2).

Future research directions

Numerous studies have supported that luteolin is a promising drug for breast cancer therapy. To push its clinical use, several issues need to be addressed and solved in the future, including (1) determining the efficacy of luteolin combined with traditional endocrine therapy, chemotherapy, and/or targeted therapy for the current and new molecular subtypes on breast cancer, (2) clinical research on the efficacy of luteolin in treatment of several subtypes of breast cancer, (3) determining whether luteolin is useful in male breast cancer, and (4) determining if luteolin is functional in novel personalized therapeutic approaches such as genomics-based therapies and immunity-based therapies.

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Conflict of interest

The authors have no conflict of interest related to this publication.

Author contributions

Wrote the manuscript and provided funds (YW, JW, and XGu); wrote the manuscript (XGo and XW); revised the manuscript for important intellectual content (XGu); contributed equally to the work and should be regarded as co-first authors (YW, JW).

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