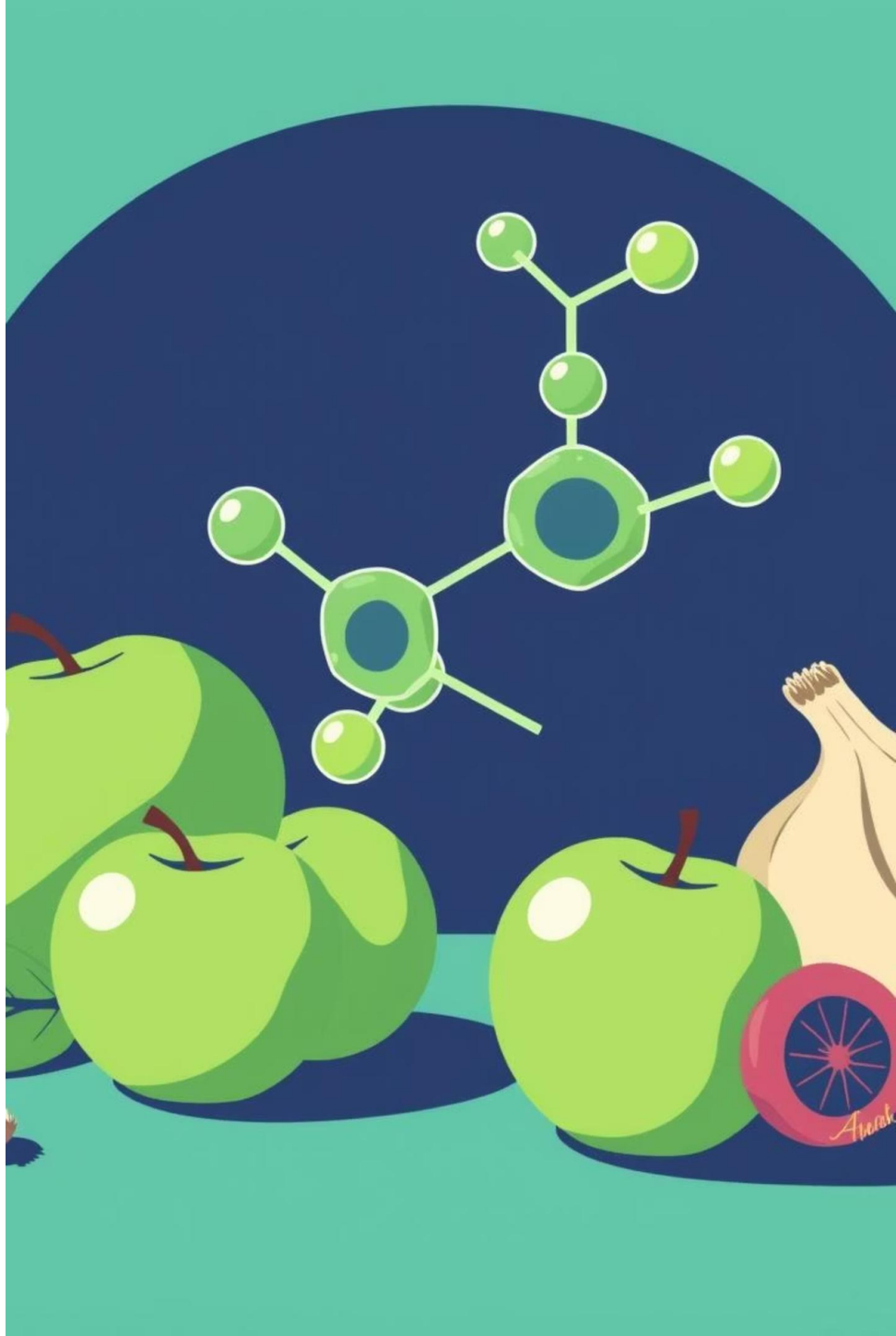
Quercetin Against Breast Cancer: Mechanisms and Therapeutic Potential

Samin Ahmadi

Medical Immunology Student



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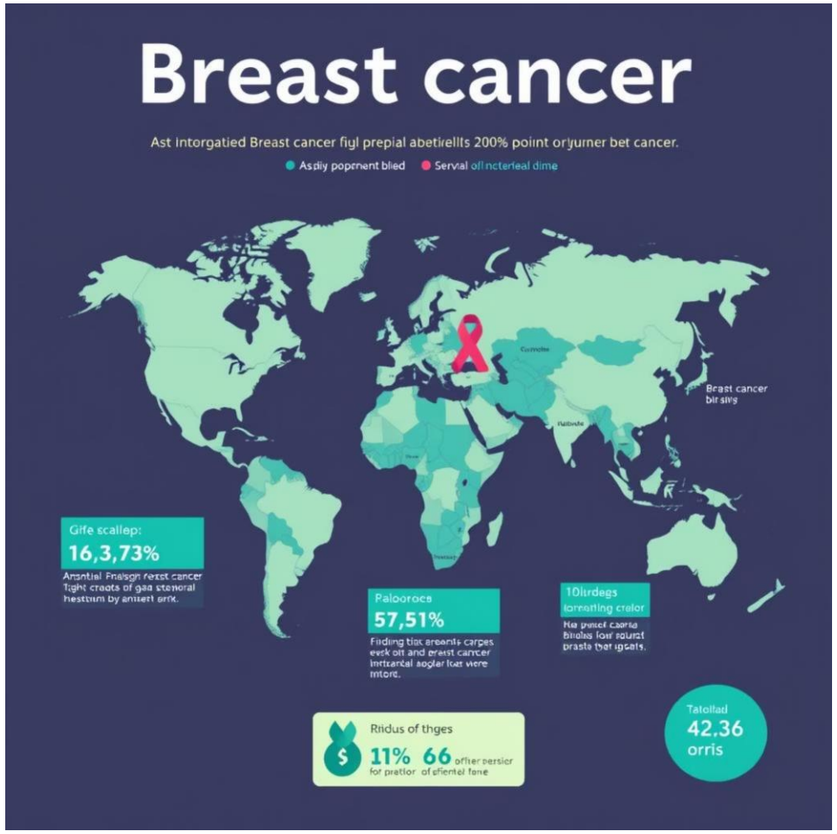
The Global Challenge of Breast Cancer

Breast cancer is the most frequently diagnosed malignancy worldwide. While mortality has declined in high-income nations due to early detection, incidence is rising in developing countries driven by population growth and lifestyle shifts.



Key Risk Factors

Genetics

Mutations in BRCA1/2, CHEK2, and PALB2 account for ~5% of cases, alongside low-penetrance SNPs.

Hormonal

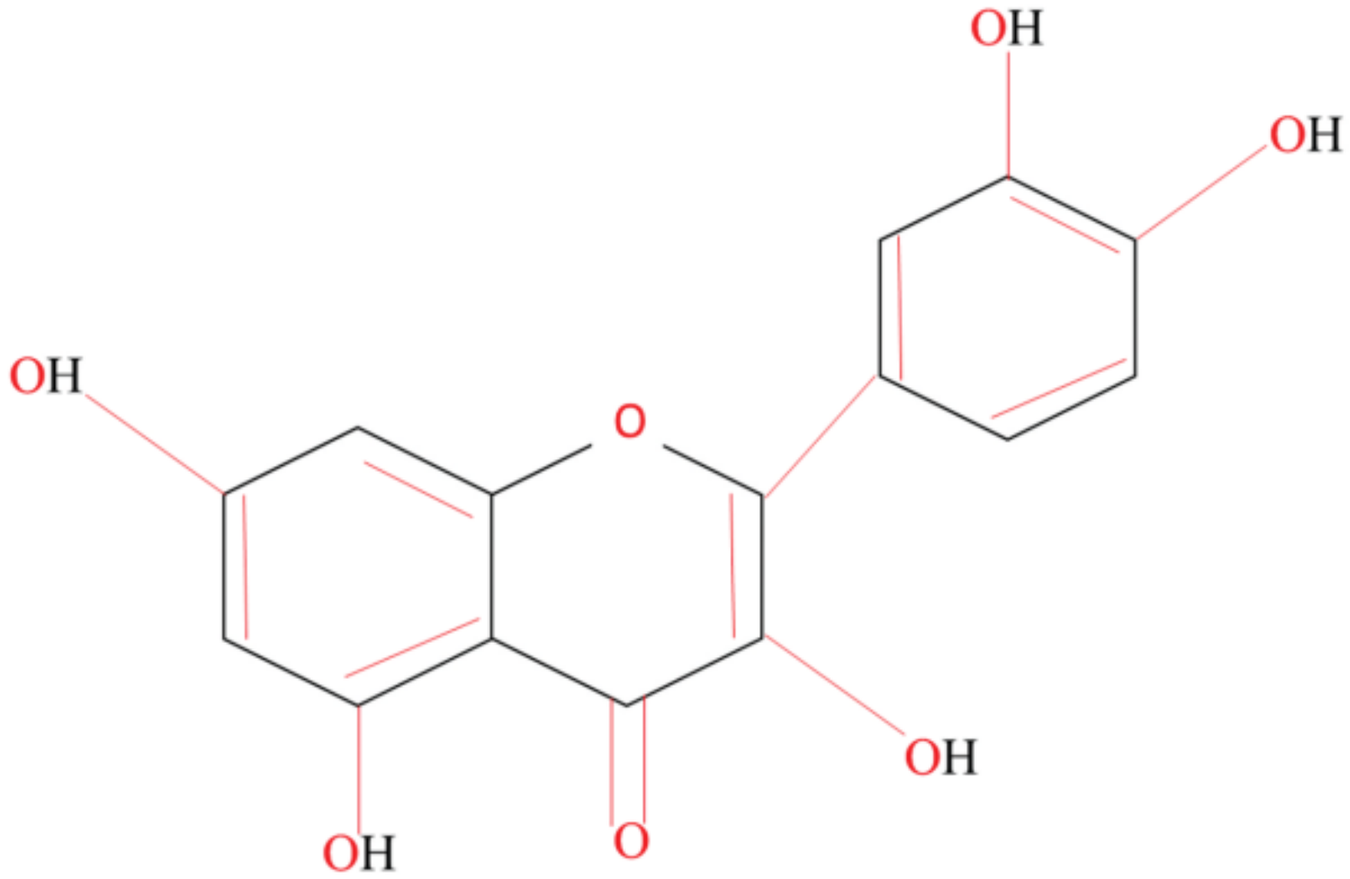
Prolonged estrogen exposure, early menarche, and late menopause increase susceptibility.

Lifestyle

Obesity, physical inactivity, alcohol consumption, and tobacco smoking are modifiable risks.

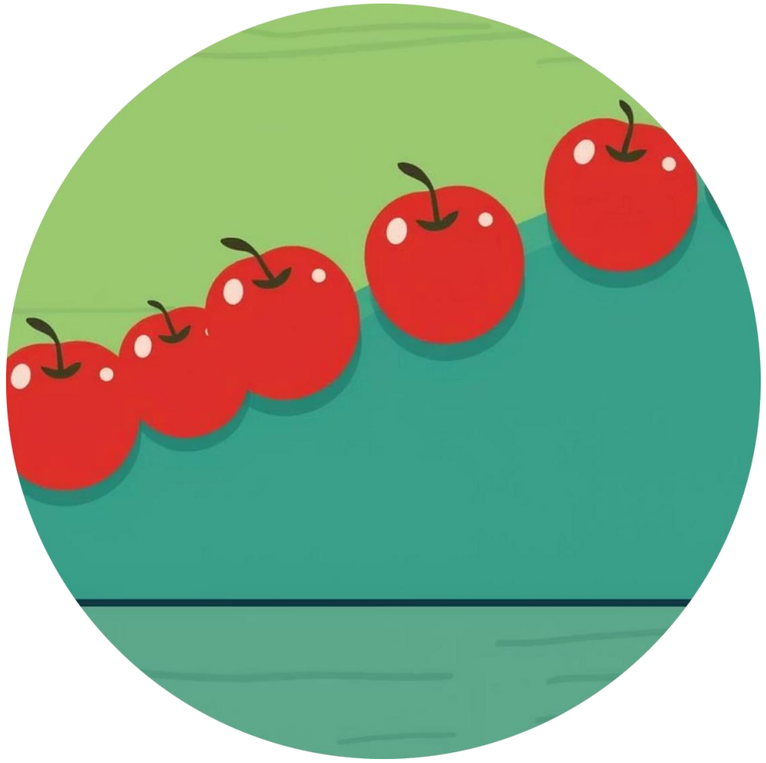
Current Standard Treatments for Breast Cancer

Effective breast cancer management relies on a multidisciplinary approach, incorporating surgery, radiotherapy, chemotherapy, and immunotherapy .Traditional cancer treatments encompass surgery, radiotherapy, chemotherapy, and immunotherapy, applied alone or in combination depending on the clinical context . Chemotherapy resistance—driven by cancer cells' adaptive responses to cytotoxic agents—remains a major impediment to therapeutic efficacy . Consequently, there is an ongoing need to develop novel adjuvant or alternative therapies.



Quercetin

Amidst the limitations of current therapies and rising interest in natural compounds, quercetin—a dietary flavonoid with potent antioxidant and anti-inflammatory properties—has attracted considerable attention for its potential anticancer effects. is well recognized for its antioxidant capacity, free radical scavenging activity, and inhibition of lipid peroxidation, all of which may contribute to its proposed chemopreventive and therapeutic roles in cancer



Apples & Berries

Rich sources of glycoside derivatives.

Onions

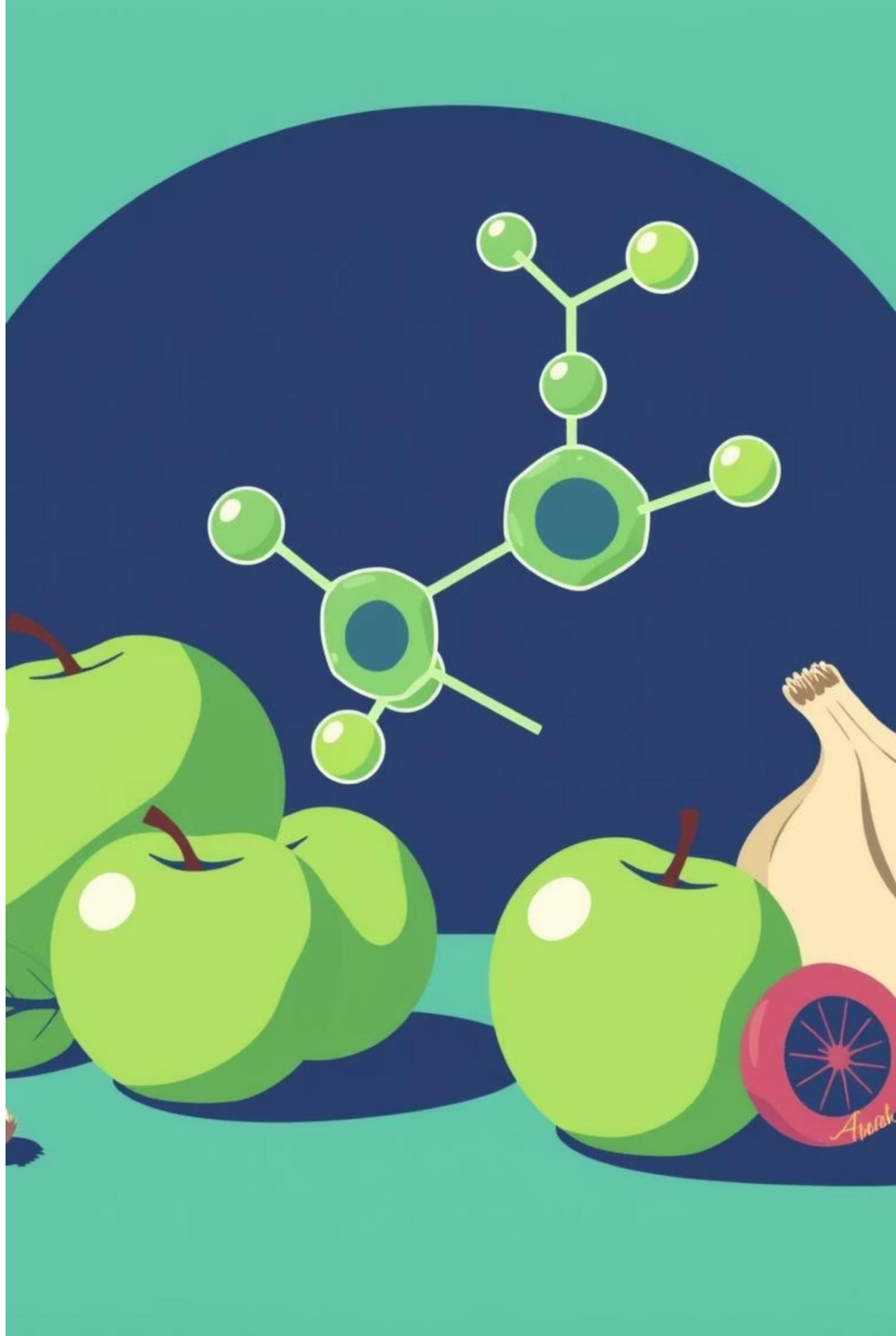
Contain high concentrations of bioavailable quercetin.

Tea & Leafy Greens

Provide a steady dietary intake of flavonoids.

Quercetin and Cell Death Signaling Pathways

The PI3K/Akt/mTOR signaling cascade is a pivotal intracellular pathway that integrates signals from nutrients, hormones, and growth factors to regulate tumor cell growth, proliferation, and survival (37, 38). Deficiency in the JNK signaling pathway has been demonstrated to promote abnormal proliferation of human mammary epithelial cells in three-dimensional culture models. Transcriptomic analyses indicate that loss of JNK pathway activity induces gene expression changes reminiscent of those triggered by activated HER2. Consistently, JNK deficiency accelerated HER2-driven breast tumorigenesis in murine models, highlighting the **tumor-suppressive role of JNK components**, some of which are mutated in human breast cancers .under conditions of EGFR overexpression or **PTEN loss, PI3K/Akt and JNK** pathways may be co-activated. This crosstalk presents promising therapeutic opportunities, where dual inhibition could synergistically improve treatment efficacy and patient outcomes, meriting further investigation



Modulating Survival: The PI3K/Akt/mTOR Pathway

The PI3K/Akt/mTOR cascade integrates signals to regulate tumor growth. Quercetin acts as a potent inhibitor of this axis, which is often constitutively active in breast cancer.

Quercetin

AKT/mTOR Block

↓ Cell Survival

PI3K Inhibition

PTEN Upregulation

↑ Apoptosis

PTEN Upregulation

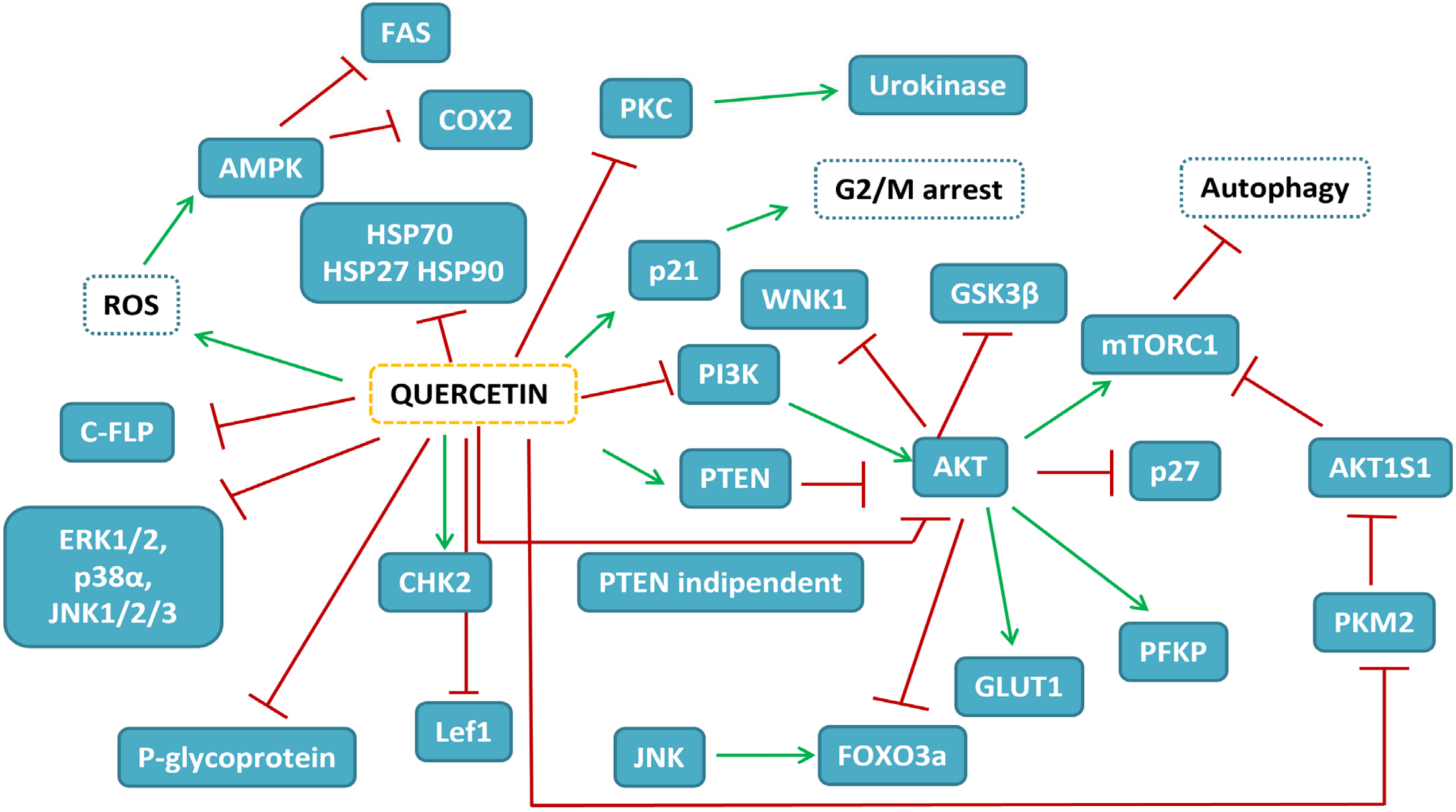
Quercetin increases the expression of the tumor suppressor PTEN, which antagonizes PI3K signaling.

Akt Suppression

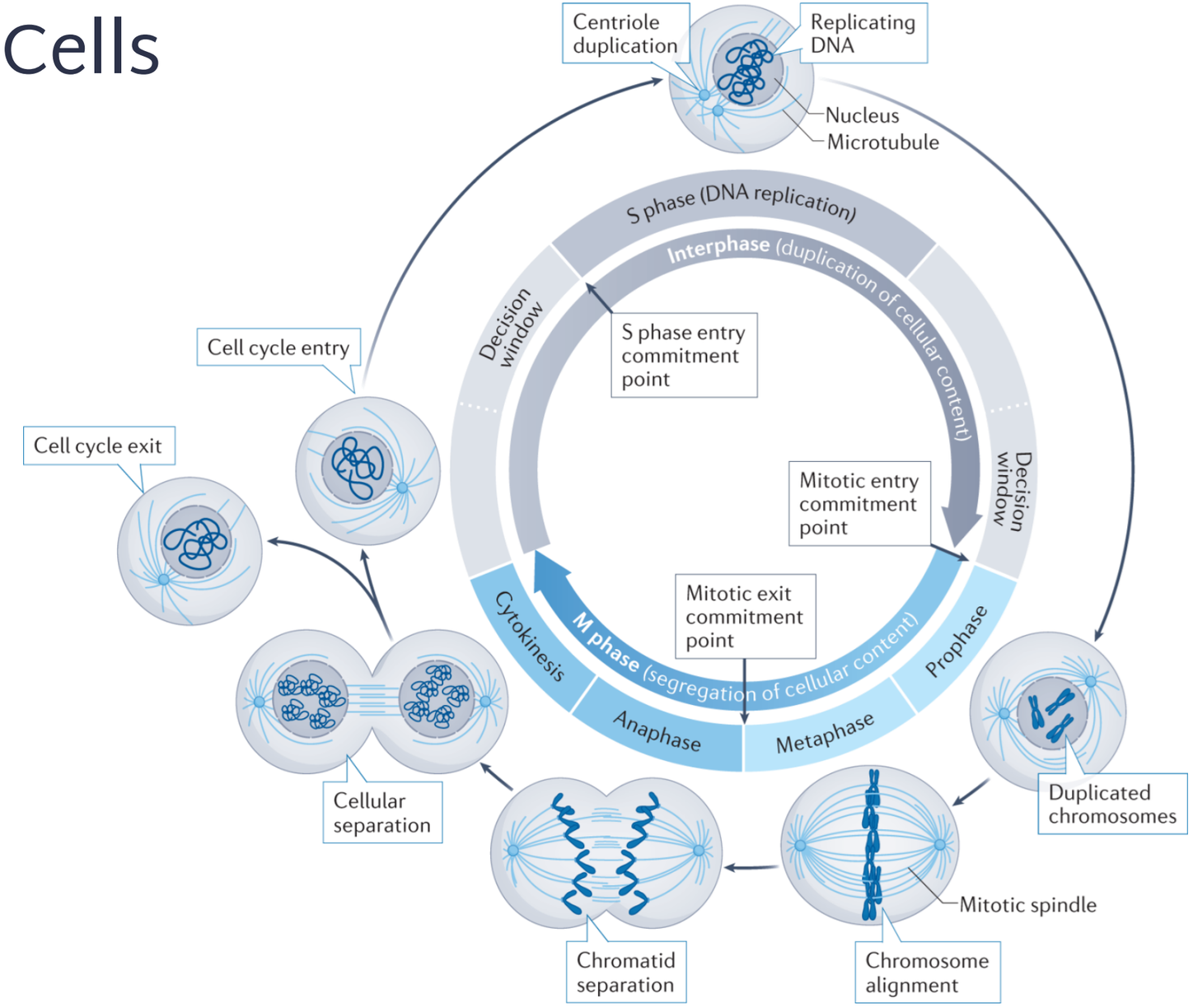
By reducing phosphorylated Akt, quercetin prevents the survival signals that drive tumor progression.

Synergistic Potential

Combining quercetin with PI3K inhibitors like LY294002 enhances apoptotic effects in MCF-7 cells.


FAS
COX2
AMPK
PKC
Urokinase
G2/M arrest
Autophagy
HSP70
HSP27 HSP90
ROS
p21
WNK1
GSK3β
mTORC1
QUERCETIN
PI3K
C-FLP
PTEN
AKT
p27
AKT1S1
ERK1/2,
p38α,
JNK1/2/3
CHK2
PTEN indipendent
PKM2
PFKP
GLUT1
Lef1
P-glycoprotein
JNK
FOXO3a

Quercetin-Induced Cell Cycle Arrest and Apoptosis in Breast Cancer Cells



Quercetin-Induced Cell Cycle Arrest and Apoptosis in Breast Cancer Cells

Quercetin has been shown to reduce viability in MDA-MB-231 breast cancer cells by inducing apoptosis and causing cell cycle arrest. At a concentration of 200 μM, quercetin significantly arrested cells at the G2/M phase and increased accumulation in the S phase, with higher doses augmenting the sub-G1 population, indicative of enhanced apoptosis. Treatment with quercetin also induced DNA damage and fragmentation. Molecular analyses revealed downregulation of cell cycle-related proteins—including **thymidylate synthase** and **cyclins A and E**—as well as **pro-caspases (-3, -8, -9, -12), XIAP, and PARP**. Conversely, markers of apoptosis and endoplasmic reticulum (ER) stress—such as ATF6α, PERK, GRP78, Bax, Fas, cytochrome c, apoptosis-inducing factor (AIF), and activated caspase-3—were significantly upregulated. Quercetin has been shown to decrease steady-state p53 protein levels without affecting p53 mRNA expression, suggesting a post-transcriptional mechanism of regulation. Specifically, quercetin inhibits p53 mRNA translation in a dose-dependent manner, resulting in reduced synthesis of newly formed p53 protein .

Halting the Cycle: G_2/M Arrest and Apoptosis

Cancer cells evade growth controls through cell cycle dysregulation. Quercetin restores control by inducing arrest and triggering programmed cell death. Interestingly, apoptosis induction appeared to occur independently of p53, as its expression remained largely unchanged. Flow cytometric analysis further confirmed increased cytosolic calcium (Ca^{2+}), supporting the involvement of ER stress in quercetin-induced apoptosis. . Quercetin treatment significantly decreased Bcl-2 levels while increasing Bax expression, indicating enhanced apoptotic activity.

In addition to modulating key protein regulators of apoptosis, quercetin also exerts its pro-apoptotic effects through epigenetic mechanisms. Notably, it has been shown to alter microRNA expression by upregulating miR-146a in both MCF-7 and MDA-MB-231 cells and downregulating miR-21 in MCF-7 cells. These microRNAs are known to influence apoptosis and cell cycle regulation, suggesting a complementary mechanism by which quercetin inhibits tumor growth.

Metabolic Effects of Quercetin in Breast Cancer

Tumor cells rely on glycolysis (the Warburg Effect) for rapid energy. Quercetin disrupts this metabolic plasticity to starve the ca

The resultant modulation of the tumor microenvironment may impede cancer cell migration, enhance apoptotic susceptibility, and reduce metastatic potential.

These metabolic disruptions position quercetin as a promising candidate for targeting the altered energy metabolism characteristic of cancer cells.

Glycolysis Inhibition

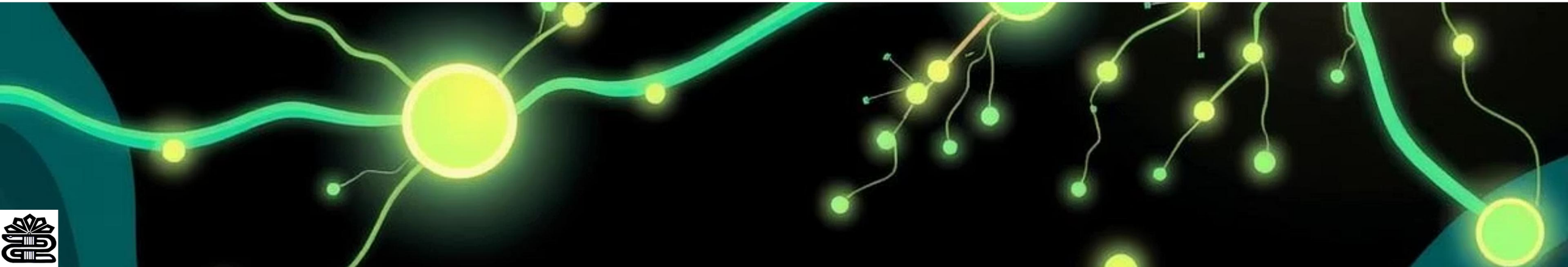
Downregulates PKM2 and LDHA enzymes, reducing energy production.

Glucose Transport

Suppresses GLUT1, limiting the glucose uptake required for tumor fuel.

Acidity Reduction

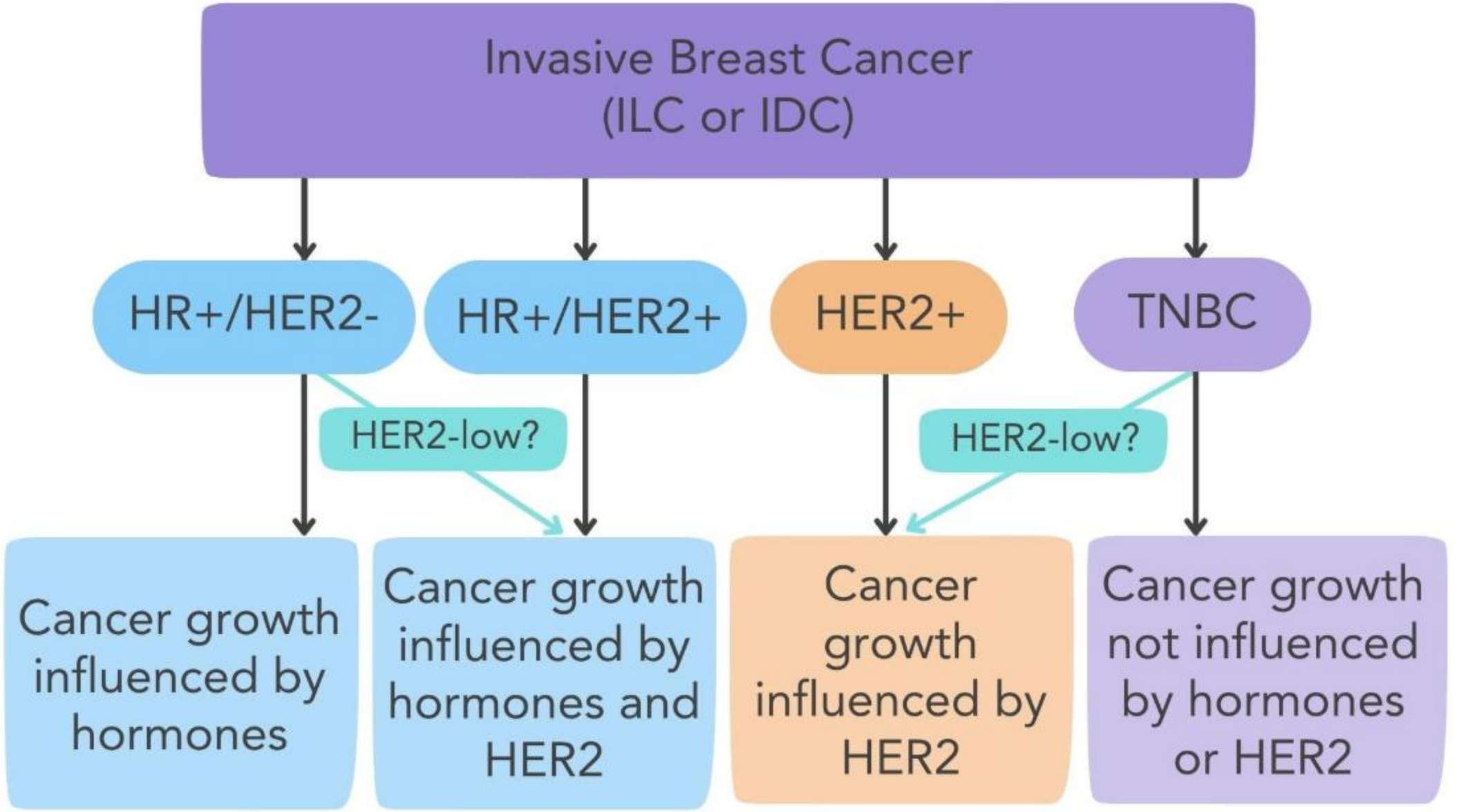
Decreases lactate production, making the microenvironment less acidic and less conducive to migration.



Preclinical and Clinical Evidence

Quercetin demonstrates versatile activity across different molecular profiles of breast cancer.

Subtype	Mechanism of Action
Triple-Negative (TNBC)	Induces G_2/M arrest, modulates mutant p53, and suppresses β-catenin signaling in MDA-MB-231 cells.
ER+ Luminal A	Upregulates p21, inhibits leptin receptor signaling, and downregulates survivin in MCF-7 cells.
Cancer Stem Cells	Inhibits mammosphere formation and reduces markers like ALDH1A1 and CXCR4 to prevent recurrence.



Limitations and Challenges

While preclinical results are compelling, several obstacles must be cleared before clinical integration.

Low Bioavailability

Poor solubility and rapid metabolism limit systemic exposure in humans.

Supra-physiological Doses

Many studies use concentrations far higher than what is achievable through diet alone.

Lack of Clinical Trials

A paucity of large-scale, randomized human trials prevents regulatory approval and standardized dosing.

Future research must focus on standardized nanoformulations and identifying predictive biomarkers for patient stratification.

Conclusion: A Multitargeted Future

Quercetin represents the future of **precision oncology**, where low-toxicity natural agents complement conventional therapies.

Multitargeted

Hits proliferation, apoptosis, and metabolism.

Low Toxicity

Natural compound with a favorable safety profile.

Synergistic

Enhances the efficacy of existing chemotherapy.

Bridging the gap from bench to bedside requires multidisciplinary collaboration and innovative delivery systems. Quercetin is poised to evolve from a nutraceutical of interest to a clinically actionable component in the fight against breast cancer.

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Thank You