Eksakta : Berkala Ilmiah Bidang MIPA
VOLUME 26 NO 04 2025, pp 440-455
ISSN : Print 1411-3724 — Online 2549-7464
DOI : https://doi.org/10.24036/eksakta/vol26-iss04/624

Eksakta
Berkala Ilmiah Bidang MIPA
http://www.eksakta.ppj.unp.ac.id/index.php/eksakta

Review

Flavonoid Role as Autophagy Modulators in Breast Cancer Treatment Strategy

Article Info

Article history :
Received September 06, 2025
Revised October 15, 2025
Accepted October 20, 2025
Published December 30, 2025
In Press

Keywords :
Flavonoid,
autophagy,
breast cancer,
apoptosis

Frans Dany[1,2*], Ade Arsianti[1*], Linda Erlina[1], Ratih Rinendyaputri[2]

[1]Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2]Center for Biomedical Research, National Research and Innovation Agency (BRIN), Cibinong, Indonesia

Abstract. Autophagy is a tightly regulated catabolic process that enables cancer cells to survive under metabolic stress and contributes to the development of chemoresistance. Targeting autophagy has therefore emerged as a promising strategy to enhance cancer therapy efficacy. Flavonoids, a diverse class of polyphenolic compounds abundantly found in plants, have gained considerable attention due to their broad-spectrum biological activities, including anticancer effects. Recent studies highlight their ability to modulate key signaling pathways involved in cell proliferation, apoptosis, and autophagy. Several flavonoids, such as fisetin, apigenin, and quercetin, exhibit roles as autophagy modulators depending on the cellular context, offering therapeutic flexibility. Their low toxicity and synergistic potential with conventional drugs underscore their relevance as adjuvant agents. This review discusses the critical role of autophagy in cancer progression and drug resistance, and examines current evidence supporting the integration of flavonoids as autophagy modulators in the design of more effective and targeted anticancer strategies, particularly in breast cancer therapy.

Corresponding Author :
Frans Dany
Master Programme in Biomedical Science, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
Email : frans.dany@ui.ac.id

1. Introduction

Autophagy, an evolutionarily conserved lysosome-dependent degradation pathway, is increasingly recognized for its dual role in cancer biology [1]. In early tumorigenesis, autophagy acts as a tumor suppressor by clearing damaged organelles and misfolded proteins; however, in established malignancies such as breast cancer, it frequently serves as a survival mechanism. Evidence indicates that autophagy supports tumor cells under metabolic stress, hypoxia, and especially in response to therapy, facilitating resistance against anticancer agents [2]. In breast cancer, upregulation of autophagy-related proteins (e.g., Beclin-1, LC3) and signaling via PI3K/AKT/mTOR and STAT3/HMGB1 pathways have been linked to reduced apoptosis after treatment, promoting drug tolerance and relapse [3-4].

Breast cancer remains a leading global health challenge. With approximately 2.3 million new diagnoses and 670,000 deaths reported in 2022, it is the most commonly diagnosed cancer in women and among the top causes of cancer mortality [5-6]. Its marked heterogeneity including luminal, HER2-positive, and triple-negative subtypes complicates treatment, especially as metastatic disease often develops multidrug resistance. Five-year survival rates for metastatic cases remain low (~30 %), underscoring the urgent need for strategies that target both tumor diversity and resistance mechanisms [7].

To overcome the limitations of conventional therapies, researchers have increasingly explored natural products—such as flavonoids, alkaloids, and terpenoids—as adjuncts or alternatives. These compounds exhibit multi-target activities, including inhibition of tumor proliferation, modulation of cell death pathways, reversal of drug efflux, and suppression of metastasis, often with reduced toxicity in normal tissues [8–10]. Among these, flavonoids have demonstrated significant potential in sensitizing resistant cancer cells and enhancing the efficacy of chemo- and targeted therapies.

Flavonoids have been reported to modulate autophagy in cancer models, either by suppressing or activating its key regulators such as PI3K/Akt/mTOR to promote autophagy-related cell death, enhance chemosensitivity, and inhibit tumor proliferation, migration, and metastasis [11–14]. However, these effects appear to be highly context-dependent, as studies in other malignancies, such as gastric and bladder cancer, suggest that certain flavonoids like quercetin may instead elicit cytoprotective autophagy, prevent apoptosis, and require autophagy inhibitor agents in order to exert anticancer effects [15-16]. This bidirectional and tumor-type–specific behavior highlights a critical gap in our understanding of how flavonoid-mediated autophagy influences breast cancer progression. Given the limited and often fragmented evidence available, the present review aims to review the role of flavonoids in autophagy modulation and its implications for breast cancer therapy. A deeper understanding of these context-specific mechanisms will not only advance our knowledge of flavonoid-modulated autophagy in breast cancer, but also facilitate the rational design of flavonoid-based therapeutics, either as standalone anticancer agents or as adjuvants that enhance the efficacy and specificity of current treatment regimens.

2. Experimental Section

2.1. Material Search Strategy

This concise review implemented a systematic literature browsing protocol. The authors conducted literature search using various sources which include PubMed, Google Scholar, Crossref and USDA food database from November 2024 to March 2025. Search strategy was divided into four main blocks with different set of relevant keywords. *The first block*: autophagy, pathway, cancer, ATG, chemoresistance, drug resistance, breast cancer, target, therapy; *second block* included: breast cancer, epidemiology, incidence, burden, Asia, GLOBOCAN, risk factor, classification, diagnosis, prognosis, marker, treatment; *third block* comprised of: flavonoid, classification, biosynthesis, biological activities, food; and *the fourth block* with: autophagy, inhibitor, blockage, breast cancer, flavonoid.

The process of selecting articles for this literature review began with the initial record identification, yielding 76 articles from the defined search strategy. An early screening of title and abstract was carried out for each selected article. This initial pool was swiftly refined by removing duplicates and other preliminary exclusions, resulting in 65 articles that progressed to the detailed screening phase. In the subsequent, more rigorous eligibility assessment, the full texts of these 65 articles were thoroughly evaluated against the inclusion and exclusion criteria. This in-depth scrutiny led to the exclusion of 10 articles due to reasons such as a lack of relevant data or other criteria. Details of exclusion criteria in each step are depicted in Table 1. Ultimately, the remaining 55 articles successfully met all quality and relevance requirements and were therefore included in the final analysis of the literature review, forming the complete evidence base for the study.

Each selected manuscript was reviewed independently and any discordance would be resolved by voting among authors. Figure 1 depicts the workflow for article selection process in this review. The decision to use narrative synthesis for this review was justified by the high level of study heterogeneity across the literature and this method is able to systematically textually summarize and interpret these diverse findings, ensuring that the mechanistic complexity is thoroughly explained rather than being oversimplified into a single statistical effect [17]. Online PRISMA tool was used to assist making the chart for this approach [18].

Table 1. Exclusion criteria of articles in this study.

Step	Criteria
Identification	Duplicate entries
	Studies were not conducted in human (*Homo sapiens*)
	Studies were conducted in cancer types other than breast carcinoma
Screening	Articles are neither in Bahasa Indonesia nor English
	Articles cannot be retrieved
	Scope of discussion is outside canonical autophagy pathways and its regulatory proteins
	Effect of multiple flavonoids in a whole extract is not evaluated separately or uncleared
	Specified flavonoids has no effect on autophagy
	Flavonoids were modified as synthetic derivatives instead of naturally occurring compounds

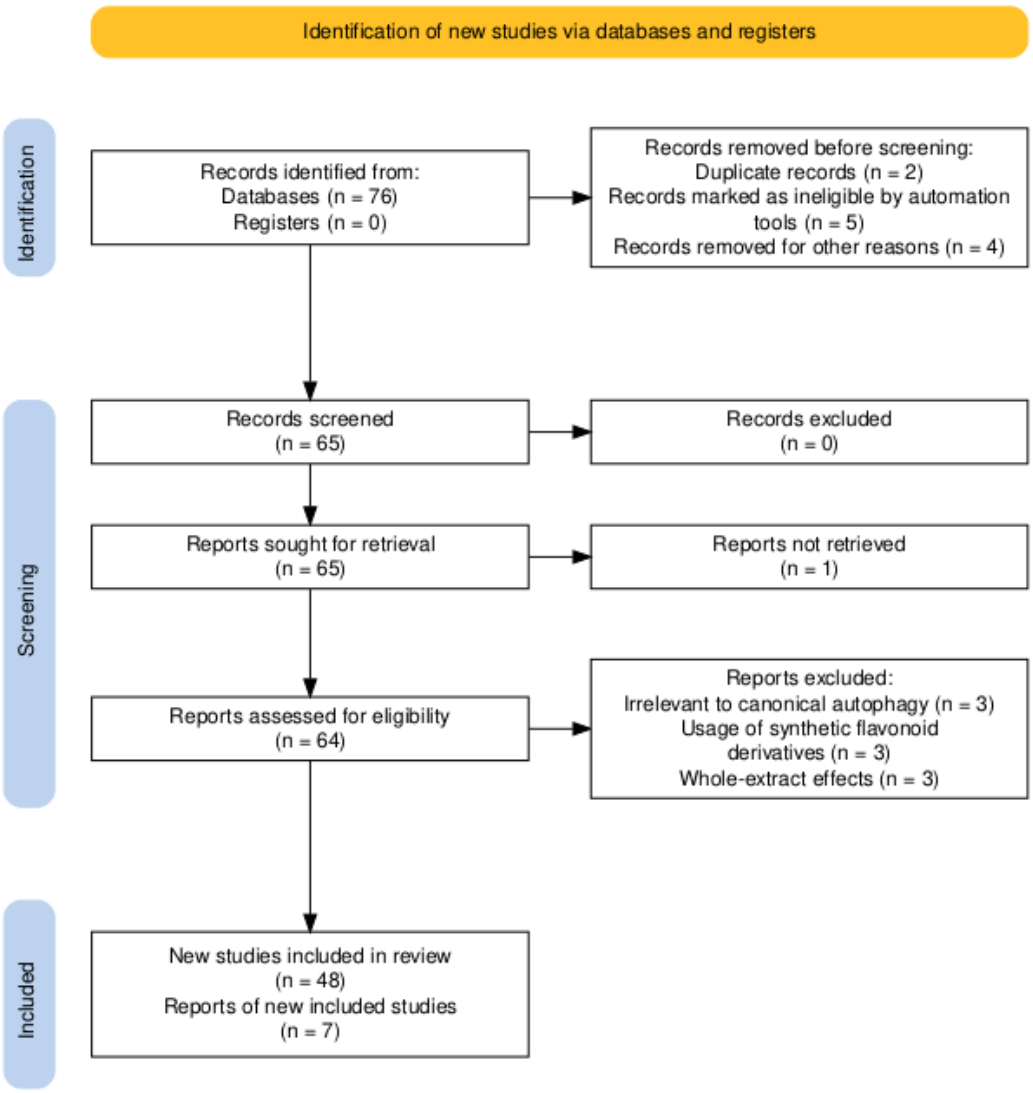

Figure 1. PRISMA chart of literature search and analysis

3. Results and Discussion

3.1. Cytoprotective Autophagy in Cancer Cell Survival and Its Potential for Targeted Therapy

Autophagy is actually a physiological attempt to promote cell survival under unfavorable conditions such as nutrition deprivation, hypoxia, and other factors by recycling intracellular constituents to sustain energy and biosynthesis [19]. However, it is often upregulated in cancer as a mechanism to protect cancer cells from various stressors, notably those induced by administration of cancer drugs. Autophagy occurs in several types, but mostly in form of macroautophagy. This begins with activation of upstream autophagy sensor, formation of phagophore—a precursor for autophagosome in a step called as nucleation, phagophore elongation, autophagosome fusion with lysosome and cargo molecule degradation by lysosomal enzymes [1]. Autophagy sequential steps is illustrated in Figure 2.

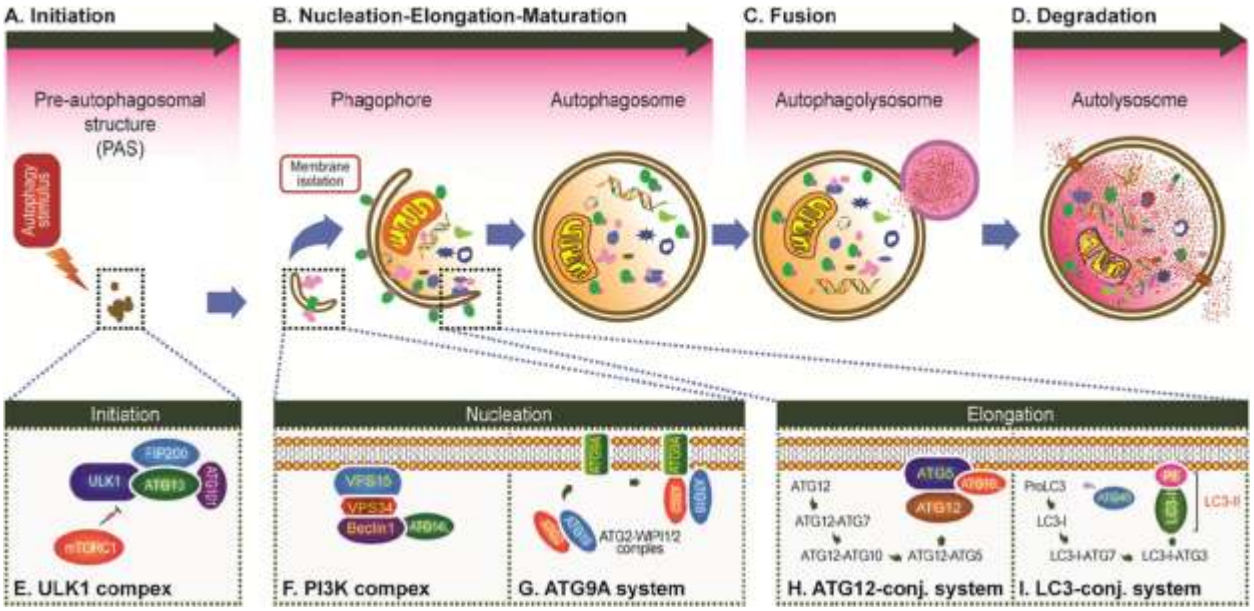

Figure 2. Phases of autophagy flux [19]

Key regulators of autophagy include: AMPK which activates autophagy in response to low ATP, mTOR; the master negative regulator whose inhibition initiates autophagy, and ULK1, which orchestrates autophagosome initiation alongside Vps34–Beclin1 nucleation complexes [19]. In nutrient-deprived or drug-challenged tumor cells, activation of AMPK and ULK1 with concomitant mTOR suppression enables cytoprotective autophagy that prevents apoptotic death. Overexpression of Beclin1 or heightened Vps34 activity further enhances this protective mechanism and correlates with poor prognosis in several cancers, including breast carcinoma [2],[20]. Another study found that autophagy induced by hypoxic environment in breast cancer stem cells contributes to their resistant phenotype. Based on these notions, targeted modulation of autophagy has emerged as a therapeutic strategy [21-22].

Early-stage inhibitors like Spautin-1 destabilize the Beclin1–Vps34 complex via USP10/13 inhibition, while ULK1 inhibitors such as SBI-0206965 suppress autophagosome formation [23-24]. MHY1485, conversely, activates mTOR to block autophagy initiation and VPS34 inhibitors (e.g., PF-03814735), late-stage lysosome inhibitors (chloroquine, hydroxychloroquine, Lys05), and PI3K-related inhibitors (Wortmannin, GW837331X) impair autophagy at nucleation or degradation stages [20],[25-26]. Obatoclax has been reported to disrupt autophagic flux by impairing lysosomal acidification [27]. Combined or sequential use of these compounds—such as SBI-0206965 with mTOR inhibitors or chloroquine with chemotherapy—has sensitized tumor cells to apoptosis in preclinical models [21-22],[26]. As promising as they are, these autophagy modulators still bear a risk of uncomfortable side effects. Hence, alternative treatment through utilization of bioactive compounds isolated from natural plants with higher safety profile, such as flavonoids, is encouraged and being developed [28-29].

3.2. Flavonoids: Chemistry, Diet, and Health

Flavonoids are polyphenolic compounds characterized by a C6–C3–C6 backbone with various hydroxylations and glycosylated forms (Figure 3). They have their name from the latin word '*flavus*' meaning yellow [30]. Common in fruits, vegetables, teas, and grains, they exhibit antioxidant, anti-inflammatory, cardiovascular, and anticancer properties, flavonoids act through ROS scavenging,

modulation of signal transduction (e.g., PI3K/AKT/mTOR, MAPK, NF-κB), epigenetic regulation, and miRNA expression [29],[31]. These yellow-by-nature compounds are categorized into several subclasses based on their chemical structure, particularly variations in the oxidation state and substitution pattern of the central C-ring [32]. These structural distinctions underpin their diverse biological activities, including antioxidant, anti-inflammatory, and anticancer potentials.

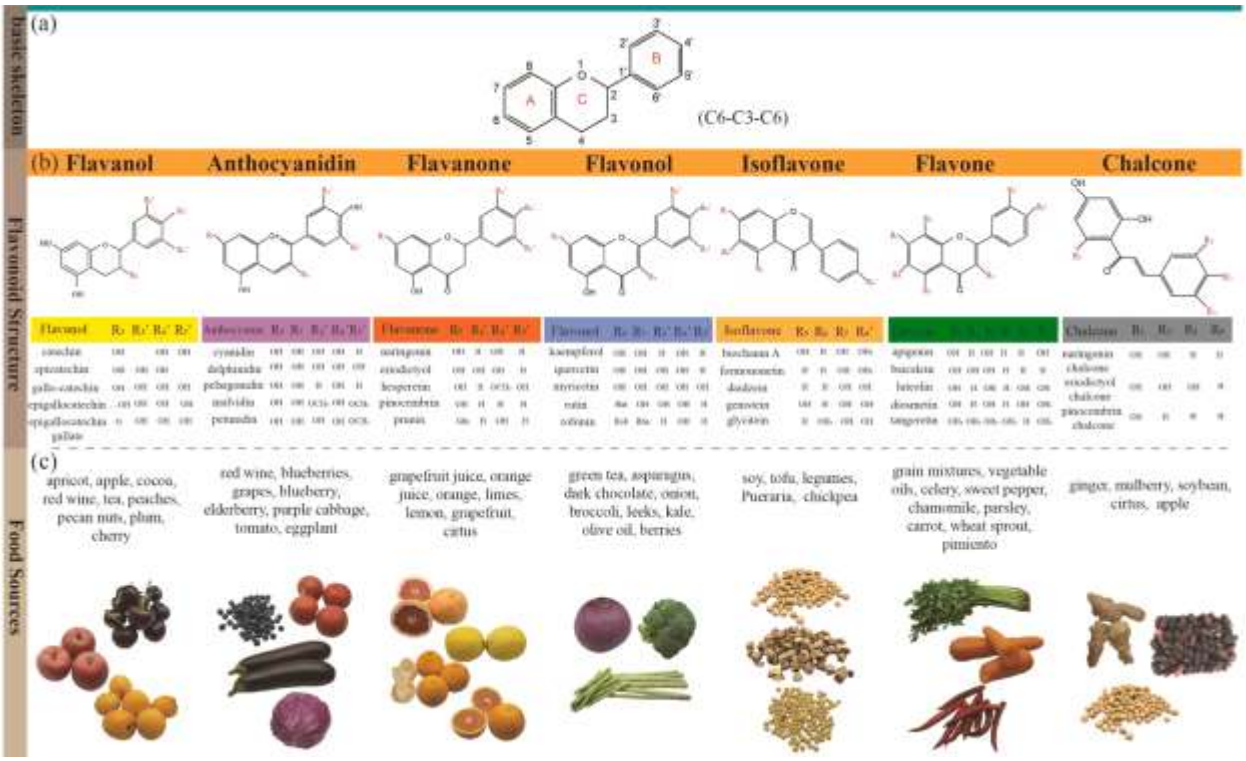

Figure 3. Flavonoid basic structure, classification and natural sources [32].

Some notable ones include anthocyanidins with a flavylium cation structure, giving rise to their vibrant pigmentation and pH-dependent color shifts. Others include strong antioxidant flavanols (e.g., catechins), flavanones commonly found in citrus fruits, flavonols with ability to chelate metals and scavenge free radicals, isoflavones that has phytoestrogenic activity due to their similarity to 17β-estradiol and so forth [32-33]. Given their abundance in nature, a considerable amount of flavonoid compounds have been identified and reviewed from our daily diet sources. Table 2 presents a list of selected major flavonoids based on Food and Nutrient Database for Dietary Studies by Food Surveys Research Group, U.S. Department of Agriculture or USDA [34].

Table 2. Classification and Examples of Dietary Flavonoids by USDA [34].

Flavonoid Class	Compound Name
Anthocyanidins	Cyanidin
	Delphinidin
	Malvidin
	Pelargonidin
	Peonidin
	Petunidin

Flavonoid Class	Compound Name
Flavan-3-ols	(-)-Epicatechin*
	(-)-Epicatechin 3-gallate*
	(-)-Epigallocatechin*
	(-)-Epigallocatechin 3-gallate*
	(+)-Catechin*
	(+)-Gallocatechin*
	Theaflavin
	Theaflavin-3,3'-digallate
	Theaflavin-3'-gallate
	Theaflavin-3-gallate
	Thearubigins
Flavanones	Eriodictyol
	Hesperetin
	Naringenin
Flavones	Apigenin
	Luteolin
Flavonols	Isorhamnetin
	Kaempferol
	Myricetin
	Quercetin
Isoflavones	Daidzein
	Genistein
	Glycitein

*Denotes catechin-type compounds commonly found in tea.

3.3. Flavonoids as Autophagy Modulators in Cancer

Increasing evidence supports flavonoid-mediated modulation of autophagy in cancer, notably as inducers and few as inhibitors or both. Flavonoids may activate autophagy in tumor cells, leading to excessive degradation of vital proteins and lessen their chance to survive. While as inhibitors, flavonoids might block autophagic recycling process and prevent cancer cells from reusing essential components like nutrition or regulatory proteins. [35-36]. A schematic molecular workflow of flavonoids in autophagy is highlighted in Figure 4 and their corresponding examples along with their proposed working mechanisms are shown in Table 3.

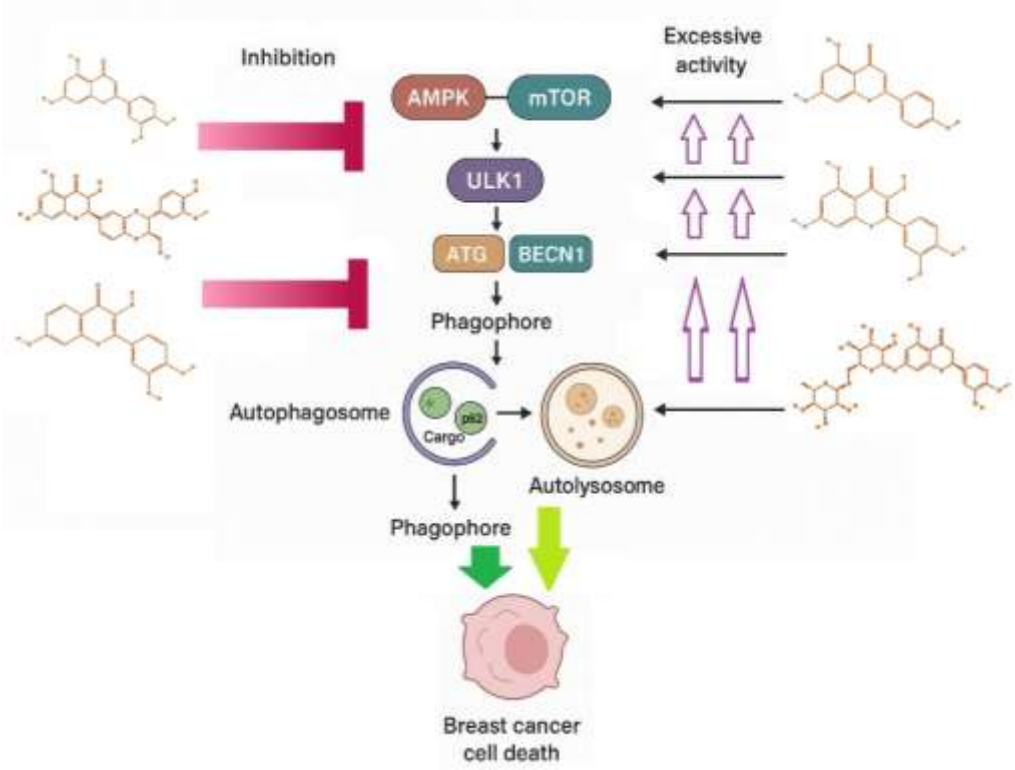

Figure 4. Role of flavonoids as autophagy modulators in breast cancer. The image was created in Biorender with some modifications in Microsoft PowerPoint and Paint.

Each of these flavonoids may have their own molecular targets and hence, diverse biological roles. Some are predominantly involved in autophagy pathways and others are tightly interconnected with other essential biological processes, most notably apoptosis [2]. As presented in Table 3, these compounds might have reciprocal effects with regard to cell survival mechanisms. Due to their antioxidant properties in nature, flavonoids can counteract oxidative stress induced by their own administration, protecting cancer cells from death. This applies in particular when reactive oxygen species (ROS)-dependent autophagy becomes the main workflow [37,38]. Some flavonoids may be combined with other drugs with opposite mechanisms in order to get similar outcomes [29].

Table 3. Flavonoids with Autophagy Modulator Potentials in Breast Cancer

Flavonoids	Class	Modulator Effects	Proposed Mechanisms
Quercetin	Flavonols	Activator	Glycolysis suppression through Akt-mTOR mediated autophagy induction in MCF-7 and MDA-MB-231 cells [39-40].
Apigenin	Flavones	Activator	T47D and MDA-MB-231 cell apoptosis when combined with autophagy inhibitor, 3-methyladenine [41].
Silibinin	Flavonolignans	Activator	ROS-dependent mitochondrial dysfunction, ATP depletion, BNIP3 upregulation in MCF-7 cells [37].

Flavonoids	Class	Modulator Effects	Proposed Mechanisms
			Downregulation of ERα, promotion of ERβ activity, caspase-independent MCF-7 cell apoptosis [37],[42].
		Inhibitor	Inducer of ROS and RNS generation in MCF-7 cells, downregulation of autophagy, negative feedback loop between redox signaling and autophagy [38].
Juglanin	Flavonols	Activator	MCF-7 cell apoptosis and autophagy via ROS/JNK signaling [43].
Baicalein	Flavones	Activator	MCF-7 and MDA-MB-231 cell apoptosis and autophagy *in vitro* and *in vivo* through inhibition of the PI3K/AKT pathway [44].
Isorhamnetin	Flavonols	Activator	Suppression of PI3K/AKT/mTOR/ULK signaling in MCF-7 and MDA-MB-231 cells [45].
Genkwanin	Flavones	Activator	Suppression of PI3K/AKT/mTOR/ULK signaling in MCF-7 and MDA-MB-231 cells [45].
Acacetin	Flavones	Activator	Suppression of PI3K/AKT/mTOR/ULK signaling in MCF-7 and MDA-MB-231 cells [45].
Warangalone	Isoflavones	Activator	Inducer of protective PINK1/Parkin-mediated mitophagy and mitochondrial apoptosis in MCF-7 and MDA-MB-231 cells [46].
Luteolin	Flavones	Activator	Downregulation of SGK1 and AKT3, FOXO3a translocation into nucleus, BNIP3 upregulation in MDA-MB-231 and 4T1 cells [47].
Delphinidin	Anthocyanidins	Activator	Suppression of mTOR pathway and activation of AMPK pathway in MDA-MB-453 and BT474 cells [48].
Myricetin	Flavonols	Activator	JNK and p38 phosphorylation, activation of Beclin-1, LC3 and Bax in SK-BR-3 cells [49].
Epigallocatechin-3-gallate	Flavan-3-ols	Activator	Inhibitor of protein arginine methyltransferase 5 (PRMT5) and enhancer of zeste homolog 2 (EZH2) in MCF-7 and MDA-MB-231 cells [50].

Flavonoids	Class	Modulator Effects	Proposed Mechanisms
			Inhibition of Hs587T cell survival signals when combined with p53 siRNA [51].
Hesperidin	Flavanones	Activator	Inducer of autophagy in silico [52]. Modulation of Bcl2/Bax pathway in MCF-7 cells [53].
Icaritin	Flavones	Inhibitor	Suppression of reactive oxygen species (ROS), autophagy blockade via estrogen receptors (ERs) and activation of AMPK in HaCaT cells [54].
Fisetin	Flavonols	Inhibitor	Inhibition of light chain 3 (LC3) conversion into LC3-II, a component critical for stable autophagosome membranes in MCF-7 cells [55].
Phloretin	Chalcones	Inhibitor	Phosphorylation of mTOR, pH-mediated inhibition of autophagy in MCF-7 and MDA-MB-231 cells [56].

Our review systematically synthesized current evidence on the role of flavonoids as autophagy modulators in breast cancer and might have revealed a certain mechanistic and subclass-specific pattern. We found that most flavonoids function as autophagy activators**,** promoting autophagy-related cell death, while only a limited subset acts as autophagy inhibitors. The majority of the identified autophagy modulators belong to the flavone and flavonol subclasses, whose characteristic structural motifs—planarity, hydroxylation at C-3, and catechol groups on the B-ring—facilitate oxidative stress induction, mitochondrial perturbation, and modulation of the PI3K/Akt/mTOR and AMPK/ULK1 signaling cascades [10,57]. These molecular signatures strongly correlate with their ability to initiate autophagy and drive programmed cell death in breast cancer cells.

3.4. Comparison with Previous Reviews

Our findings align with earlier systematic reviews, such as those by Silva et al. [57] and Hosseinzadeh et al. [10], which concluded that flavonoids commonly induce autophagy through PI3K/Akt/mTOR inhibition and AMPK activation. However, the novelty of this review lies in its quantitative subclass analysis and focused evaluation within breast cancer models, revealing that flavones and flavonols constitute the predominant autophagy-inducing groups. Previous works discussed autophagy modulation broadly across cancers but did not delineate structural subclass trends or dominance patterns specific to breast tissue [29],[35].

Furthermore, our synthesis integrates recent mechanistic discoveries that extend beyond canonical signaling pathways. Notably, we highlight the epigenetic dimension of flavonoid action, where compounds such as quercetin and apigenin modulate histone methyltransferases EZH2 and PRMT5 and alter acetylation states to promote autophagy-related gene expression [50],[58]. This multi-layered regulation—combining signal transduction, redox, and epigenetic control—represents a conceptual advance beyond previous reviews limited to cytoplasmic signaling.

3.5. Mechanistic Convergence and Context Dependency

Despite the predominance of autophagy activation, several flavonoids exhibit context-dependent dual effects**.** For example, phloretin, a dihydrochalcone, inhibits cytoprotective autophagy and enhances chemosensitivity in glucose-deprived breast cancer cells [56]. Similarly, silibinin shows both cytoprotective and pro-death autophagic responses depending on concentration and co-treatment conditions [42],[59]. These observations underscore that autophagy modulation by flavonoids is not unidirectional but highly contingent on cellular metabolic status, redox balance, and drug context**.** Such duality complicates translational development but also offers therapeutic flexibility: selective enhancement of cytotoxic autophagy or suppression of pro-survival autophagy could be tuned via structure-guided modification or combination therapy design [35],[60].

3.6. Consistency, Contradictions, and Novel Insights

Overall, our findings are consistent with the majority of contemporary evidence suggesting that flavonoids trigger autophagic cell death in breast cancer cells [11],[29],[35],[57],[61]. However, discrepancies exist with studies interpreting autophagy as a cytoprotective adaptation, particularly under hypoxia or chronic stress. These contradictions likely arise from methodological limitations, such as failure to assess autophagic flux or reliance on static markers (LC3-II, Beclin-1) [62]. Our review emphasizes that accurate differentiation between autophagy induction and flux blockade requires dynamic assays using p62/SQSTM1 turnover, lysosomal inhibitors, and tandem LC3 reporters—an analytical refinement that prior reviews often overlooked [63]. This methodological critique represents another novel contribution of the present review, providing a framework for interpreting autophagy endpoints more rigorously in future chemotherapeutic studies involving flavonoids.

3.7. Limitations and Future Research Directions

Our analysis also revealed field-level limitations that warrant systematic correction. Most available studies are in vitro, often conducted at supra-physiological concentrations, with limited pharmacokinetic validation. In vivo investigations remain scarce, and differences among breast cancer subtypes (ER+, HER2+, TNBC) are seldom addressed. Furthermore, mechanistic studies rarely integrate multi-omics profiling**,** leaving cross-talk between autophagy, apoptosis, and metabolic rewiring insufficiently understood. Hence, future research topics may:

1. Apply standardized autophagic flux assays to resolve cytoprotective vs cytotoxic outcomes [63]
2. Conduct in vivo subtype-specific evaluations of flavonoids under clinically relevant exposure levels [61],[64]
3. Integrate epigenomic and proteomic profiling to map autophagy networks [65]
4. Develop pharmacokinetically improved analogs or nanoparticle formulations to overcome poor solubility and stability [66]
5. Explore combination strategies between flavonoids and autophagy modulators (e.g., chloroquine or VPS34 inhibitors) using sequential dosing to enhance therapeutic selectivity [60]

3.8. Implications for Chemistry Education and Translational Research

Beyond oncological relevance, this review also contributes meaningfully to chemistry education, particularly in illustrating how structure–activity relationships (SAR) guide biological function and therapeutic application. By correlating specific stereochemical features, i.e., hydroxylation patterns, conjugation, and glycosylation, with autophagy modulation, the review offers a clear case study for integrating organic chemistry, biochemistry, and pharmacology in education [67]. This integrative framework can serve as a didactic model in medicinal chemistry curricula, emphasizing that natural product chemistry extends beyond isolation and characterization to encompass dynamic biological

network modulation. Such interdisciplinary connections not only enrich chemical education but also inspire rational design of next-generation autophagy-modulating therapeutics [67-68].

4. Conclusion

In summary, our review underscores that flavones and flavonols dominate as autophagy activators in breast cancer, primarily inducing autophagy-related cell death through AMPK/mTOR signaling, ROS generation, and epigenetic modulation. Only few act as autophagy inhibitors and silibinin might have dual modulation effect. This subclass-specific dominance and mechanistic breadth represent novel insights that expand upon prior literature. By integrating mechanistic, structural, and educational perspectives, this review contributes to the scientific understanding of autophagy modulation, utilization of structure–function reasoning in breast cancer drug development, and to the pedagogical advancement in chemical and pharmaceutical sciences.

References

[1] Rakesh, R., PriyaDharshini, L. C., Sakthivel, K. M., & Rasmi, R. R. (2022). Role and regulation of autophagy in cancer. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1868*(7), 166400.

[2] Debnath, J., Gammoh, N., & Ryan, K. M. (2023). Autophagy and autophagy-related pathways in cancer. *Nature reviews Molecular cell biology*, *24*(8), 560-575.

[3] Dong, C., Wu, J., Chen, Y., Nie, J., & Chen, C. (2021). Activation of PI3K/AKT/mTOR pathway causes drug resistance in breast cancer. *Frontiers in pharmacology*, *12*, 628690.

[4] Yang, B., Li, G., Wang, S., Zheng, Y., Zhang, J., Pan, B., ... & Wang, Z. (2024). Tumor-associated macrophages/CXC motif chemokine ligand 1 promotes breast cancer autophagy-mediated chemoresistance via IGF1R/STAT3/HMGB1 signaling. *Cell death & disease*, *15*(10), 743.

[5] Chhikara, B. S., & Parang, K. (2023). Global Cancer Statistics 2022: the trends projection analysis. *Chemical Biology Letters*, *10*(1), 451-451.

[6] Fu, M., Peng, Z., Wu, M., Lv, D., Li, Y., & Lyu, S. (2025). Current and future burden of breast cancer in Asia: A GLOBOCAN data analysis for 2022 and 2050. *The Breast*, *79*, 103835.

[7] Łukasiewicz, S., Czeczelewski, M., Forma, A., Baj, J., Sitarz, R., & Stanisławek, A. (2021). Breast cancer—epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—an updated review. *Cancers*, *13*(17), 4287.

[8] Mohammad, S. I., Vasudevan, A., Nadhim Mohammed, S., Uthirapathy, S., MM, R., Kundlas, M., ... & Ali Hussein, Z. (2025). Anti-metastatic potential of flavonoids for the treatment of cancers: focus on epithelial-mesenchymal transition (EMT) process. *Naunyn-Schmiedeberg's Archives of Pharmacology*, 1-27.

[9] Pyo, Y., Kwon, K. H., & Jung, Y. J. (2024). Anticancer potential of flavonoids: their role in cancer prevention and health benefits. *Foods*, *13*(14), 2253.

[10] Hosseinzadeh, A., Poursoleiman, F., Biregani, A. N., & Esmailzadeh, A. (2023). Flavonoids target different molecules of autophagic and metastatic pathways in cancer cells. *Cancer Cell International*, *23*(1), 114.

[11] Wang, S., Wang, K., Li, C., Chen, J., & Kong, X. (2024). Role of flavonoids in inhibiting triple-negative breast cancer. *Frontiers in Pharmacology*, *15*, 1411059.

[12] Elsori, D., Pandey, P., Ramniwas, S., Kumar, R., Lakhanpal, S., Rab, S. O., ... & Khan, F. (2024). Naringenin as potent anticancer phytocompound in breast carcinoma: from mechanistic approach to nanoformulations based therapeutics. *Frontiers in pharmacology*, *15*, 1406619.

[13] Yuan, C., Chen, G., Jing, C., Liu, M., Liang, B., Gong, G., & Yu, M. (2022). Eriocitrin, a dietary flavonoid suppressed cell proliferation, induced apoptosis through modulation of

JAK2/STAT3 and JNK/p38 MAPKs signaling pathway in MCF-7 cells. *Journal of Biochemical and Molecular Toxicology*, *36*(1), e22943.

[14] Mazurakova, A., Koklesova, L., Samec, M., Kudela, E., Kajo, K., Skuciova, V., ... & Kubatka, P. (2022). Anti-breast cancer effects of phytochemicals: primary, secondary, and tertiary care. *EPMA Journal*, *13*(2), 315-334.

[15] Wang, K., Liu, R., Li, J., Mao, J., Lei, Y., Wu, J., ... & Wei, Y. (2011). Quercetin induces protective autophagy in gastric cancer cells: involvement of Akt-mTOR-and hypoxia-induced factor 1α-mediated signaling. *Autophagy*, *7*(9), 966-978.

[16] Tsai, T. F., Thomas, I., Hwang, S., Lin, J. F., Chen, H. E., Yang, S. C., ... & Chou, K. Y. (2019). Suppression of quercetin-induced autophagy enhances cytotoxicity through elevating apoptotic cell death in human bladder cancer cells. *Urological Science*, *30*(2), 58-66.

[17] Campbell, M., Katikireddi, S. V., Sowden, A., McKenzie, J. E., & Thomson, H. (2018). Improving Conduct and Reporting of Narrative Synthesis of Quantitative Data (ICONS-Quant): protocol for a mixed methods study to develop a reporting guideline. *BMJ open*, *8*(2), e020064.

[18] Haddaway, N. R., Page, M. J., Pritchard, C. C., & McGuinness, L. A. (2022). PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and Open Synthesis. *Campbell systematic reviews*, *18*(2), e1230.

[19] Li, X., He, S., & Ma, B. (2020). Autophagy and autophagy-related proteins in cancer. *Molecular cancer*, *19*(1), 12.

[20] Abd El-Aziz, Y. S., Gillson, J., Jansson, P. J., & Sahni, S. (2022). Autophagy: a promising target for triple negative breast cancers. *Pharmacological Research*, *175*, 106006.

[21] Bousquet, G., El Bouchtaoui, M., Sophie, T., Leboeuf, C., de Bazelaire, C., Ratajczak, P., ... & Janin, A. (2017). Targeting autophagic cancer stem-cells to reverse chemoresistance in human triple negative breast cancer. *Oncotarget*, *8*(21), 35205.

[22] Hassan, A. M. I. A., Zhao, Y., Chen, X., & He, C. (2024). Blockage of autophagy for cancer therapy: A comprehensive review. *International journal of molecular sciences*, *25*(13), 7459.

[23] Kona, S. V., & Kalivendi, S. V. (2024). The USP10/13 inhibitor, spautin-1, attenuates the progression of glioblastoma by independently regulating RAF-ERK mediated glycolysis and SKP2. *Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1870*(7), 167291.

[24] Tang, F., Hu, P., Yang, Z., Xue, C., Gong, J., Sun, S., ... & Xie, C. (2017). SBI0206965, a novel inhibitor of Ulk1, suppresses non-small cell lung cancer cell growth by modulating both autophagy and apoptosis pathways. *Oncology reports*, *37*(6), 3449-3458.

[25] Di Donato, M., Giovannelli, P., Migliaccio, A., & Bilancio, A. (2022). Inhibition of Vps34 and p110δ PI3K impairs migration, invasion and three-dimensional spheroid growth in breast cancer cells. *International Journal of Molecular Sciences*, *23*(16), 9008.

[26] Chicote, J., Yuste, V. J., Boix, J., & Ribas, J. (2020). Cell death triggered by the autophagy inhibitory drug 3-methyladenine in growing conditions proceeds with DNA damage. *Frontiers in Pharmacology*, *11*, 580343.

[27] Schwartz-Roberts, J. L., Shajahan, A. N., Cook, K. L., Wärri, A., Abu-Asab, M., & Clarke, R. (2013). GX15-070 (Obatoclax) Induces Apoptosis and Inhibits Cathepsin D-and L–Mediated Autophagosomal Lysis in Antiestrogen-Resistant Breast Cancer Cells. *Molecular cancer therapeutics*, *12*(4), 448-459.

[28] Liu, F., Zhao, L., Wu, T., Yu, W., Li, J., Wang, W., ... & Xu, Y. (2024). Targeting autophagy with natural products as a potential therapeutic approach for diabetic microangiopathy. *Frontiers in Pharmacology*, *15*, 1364616.

[29] Ponte, L. G. S., Pavan, I. C. B., Mancini, M. C. S., da Silva, L. G. S., Morelli, A. P., Severino, M. B., ... & Simabuco, F. M. (2021). The hallmarks of flavonoids in cancer. *Molecules*, *26*(7), 2029.

[30] Bone, K., & Mills, S. (2013). *Principles and practice of phytotherapy: modern herbal medicine*. Elsevier Health Sciences.

[31] Tang, S., Wang, B., Liu, X., Xi, W., Yue, Y., Tan, X., ... & Huang, L. (2025). Structural insights and biological activities of flavonoids: Implications for novel applications. *Food Frontiers*, *6*(1), 218-247.

[32] Shen, N., Wang, T., Gan, Q., Liu, S., Wang, L., & Jin, B. (2022). Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. *Food chemistry*, *383*, 132531.

[33] Chen, S., Wang, X., Cheng, Y., Gao, H., & Chen, X. (2023). A review of classification, biosynthesis, biological activities and potential applications of flavonoids. *Molecules*, *28*(13), 4982.

[34] Haytowitz, D. B., Wu, X., & Bhagwat, S. (2018). USDA database for the flavonoid content of selected foods, release 3.3. *US Department of Agriculture*, *173*.

[35] Zhang, Z., Shi, J., Nice, E. C., Huang, C., & Shi, Z. (2021). The multifaceted role of flavonoids in cancer therapy: leveraging autophagy with a double-edged sword. *Antioxidants*, *10*(7), 1138.

[36] Silva-Pinto, P. A., de Pontes, J. T. C., Aguilar-Morón, B., Canales, C. S. C., Pavan, F. R., & Roque-Borda, C. A. (2025). Phytochemical insights into flavonoids in cancer: Mechanisms, therapeutic potential, and the case of quercetin. *Heliyon*, *11*(4).

[37] Jiang, K., Wang, W., Jin, X., Wang, Z., Ji, Z., & Meng, G. (2015). Silibinin, a natural flavonoid, induces autophagy via ROS-dependent mitochondrial dysfunction and loss of ATP involving BNIP3 in human MCF7 breast cancer cells. *Oncology reports*, *33*(6), 2711-2718.

[38] Zheng, N., Liu, L., Liu, W. W., Li, F., Hayashi, T., Tashiro, S. I., ... & Ikejima, T. (2017). Crosstalk of ROS/RNS and autophagy in silibinin-induced apoptosis of MCF-7 human breast cancer cells in vitro. *Acta Pharmacologica Sinica*, *38*(2), 277-289.

[39] Tang, S. M., Deng, X. T., Zhou, J., Li, Q. P., Ge, X. X., & Miao, L. (2020). Pharmacological basis and new insights of quercetin action in respect to its anti-cancer effects. *Biomedicine & Pharmacotherapy*, *121*, 109604.

[40] Jia, L., Huang, S., Yin, X., Zan, Y., Guo, Y., & Han, L. (2018). Quercetin suppresses the mobility of breast cancer by suppressing glycolysis through Akt-mTOR pathway mediated autophagy induction. *Life sciences*, *208*, 123-130.

[41] Cao, X., Liu, B., Cao, W., Zhang, W., Zhang, F., Zhao, H., ... & Zhang, B. (2013). Autophagy inhibition enhances apigenin-induced apoptosis in human breast cancer cells. *Chinese Journal of Cancer Research*, *25*(2), 212.

[42] Liu, W., Ji, Y., Sun, Y., Si, L., Fu, J., Hayashi, T., ... & Ikejima, T. (2020). Estrogen receptors participate in silibinin-caused nuclear translocation of apoptosis-inducing factor in human breast cancer MCF-7 cells. *Archives of Biochemistry and Biophysics*, *689*, 108458.

[43] Wang, S., Wang, K., Wang, H., Han, J., & Sun, H. (2017). Autophagy is essential for flavopiridol-induced cytotoxicity against MCF-7 breast cancer cells. *Molecular Medicine Reports*, *16*(6), 9715-9720.

[44] Yan, W., Ma, X., Zhao, X., & Zhang, S. (2018). Baicalein induces apoptosis and autophagy of breast cancer cells via inhibiting PI3K/AKT pathway in vivo and vitro. *Drug design, development and therapy*, 3961-3972.

[45] Zhang, H. W., Hu, J. J., Fu, R. Q., Liu, X., Zhang, Y. H., Li, J., ... & Gao, N. (2018). Flavonoids inhibit cell proliferation and induce apoptosis and autophagy through downregulation of PI3Kγ mediated PI3K/AKT/mTOR/p70S6K/ULK signaling pathway in human breast cancer cells. *Scientific reports*, *8*(1), 11255.

[46] Mao, L., Liu, H., Zhang, R., Deng, Y., Hao, Y., Liao, W., ... & Sun, S. (2021). PINK1/Parkin-mediated mitophagy inhibits warangalone-induced mitochondrial apoptosis in breast cancer cells. *Aging (Albany NY)*, *13*(9), 12955.

[47] Wu, L., Lin, Y., Gao, S., Wang, Y., Pan, H., Wang, Z., ... & Xu, Y. (2023). Luteolin inhibits triple-negative breast cancer by inducing apoptosis and autophagy through SGK1-FOXO3a-BNIP3 signaling. *Frontiers in Pharmacology*, *14*, 1200843.

[48] Chen, J., Zhu, Y., Zhang, W., Peng, X., Zhou, J., Li, F., ... & Yu, X. (2018). Delphinidin induced protective autophagy via mTOR pathway suppression and AMPK pathway activation in HER-2 positive breast cancer cells. *BMC cancer*, *18*(1), 342.

[49] Han, S. H., Lee, J. H., Woo, J. S., Jung, G. H., Jung, S. H., Han, E. J., ... & Jung, J. Y. (2022). Myricetin induces apoptosis through the MAPK pathway and regulates JNK-mediated autophagy in SK-BR-3 cells. *International journal of molecular medicine*, *49*(4), 54.

[50] Nalla, K., Chatterjee, B., Poyya, J., Swain, A., Ghosh, K., Pan, A., ... & Kanade, S. R. (2025). Epigallocatechin-3-gallate inhibit the protein arginine methyltransferase 5 and Enhancer of Zeste homolog 2 in breast cancer both in vitro and in vivo. *Archives of Biochemistry and Biophysics*, *763*, 110223.

[51] Braicu, C., Pileczki, V., Pop, L., Petric, R. C., Chira, S., Pointiere, E., ... & Berindan-Neagoe, I. (2015). Dual targeted therapy with p53 siRNA and Epigallocatechingallate in a triple negative breast cancer cell model. *PLoS One*, *10*(4), e0120936.

[52] Anggoro, B., Kumara, D., Angelina, D., & Ikawati, M. (2021). Citrus flavonoids from Citrus reticulata peels potentially target an autophagy modulator, MAP1LC3A, in breast cancer. *Indonesian Journal of Cancer Chemoprevention*, *12*(3), 114-122.

[53] Önder, G. Ö., Göktepe, Ö., Baran, M., Bitgen, N., Aydın, F., & Yay, A. (2023). Therapeutic potential of hesperidin: apoptosis induction in breast cancer cell lines. *Food and Chemical Toxicology*, *176*, 113791.

[54] Zou, J., Xu, M. X., Li, F., Wang, Y. H., Li, X. Q., Yu, D. J., ... & Sun, X. D. (2022). Icaritin alleviates docetaxel-induced skin injury by suppressing reactive oxygen species via estrogen receptors. *Thoracic Cancer*, *13*(2), 190-201.

[55] Yang, P. M., Tseng, H. H., Peng, C. W., Chen, W. S., & Chiu, S. J. (2012). Dietary flavonoid fisetin targets caspase-3-deficient human breast cancer MCF-7 cells by induction of caspase-7-associated apoptosis and inhibition of autophagy. *International journal of oncology*, *40*(2), 469-478.

[56] Chen, M., Gowd, V., Wang, M., Chen, F., & Cheng, K. W. (2021). The apple dihydrochalcone phloretin suppresses growth and improves chemosensitivity of breast cancer cells via inhibition of cytoprotective autophagy. *Food & Function*, *12*(1), 177-190.

[57] de Sousa Silva, G. V., Lopes, A. L. V. F. G., Viali, I. C., Lima, L. Z. M., Bizuti, M. R., Haag, F. B., & Tavares de Resende e Silva, D. (2023). Therapeutic properties of flavonoids in treatment of cancer through autophagic modulation: a systematic review. *Chinese Journal of Integrative Medicine*, *29*(3), 268-279.

[58] Selmin, O. I., Donovan, M. G., Stillwater, B. J., Neumayer, L., & Romagnolo, D. F. (2020). Epigenetic regulation and dietary control of triple negative breast cancer. *Frontiers in nutrition*, *7*, 159.

[59] Zheng, N., Zhang, P., Huang, H., Liu, W., Hayashi, T., Zang, L., ... & Ikejima, T. (2015). ERα down-regulation plays a key role in silibinin-induced autophagy and apoptosis in human breast cancer MCF-7 cells. *Journal of pharmacological sciences*, *128*(3), 97-107.

[60] Liu, T., Zhang, J., Li, K., Deng, L., & Wang, H. (2020). Combination of an autophagy inducer and an autophagy inhibitor: a smarter strategy emerging in cancer therapy. *Frontiers in pharmacology*, *11*, 408.

[61] Hussain, Y., Khan, H., Alam, W., Aschner, M., Abdullah, Alsharif, K. F., & Saso, L. (2022). Flavonoids Targeting the mTOR Signaling Cascades in Cancer: A Potential Crosstalk in Anti-Breast Cancer Therapy. *Oxidative Medicine and Cellular Longevity*, *2022*(1), 4831833.

[62] Yoshii, S. R., & Mizushima, N. (2017). Monitoring and measuring autophagy. *International journal of molecular sciences*, *18*(9), 1865.

[63] Mizushima, N., & Murphy, L. O. (2020). Autophagy assays for biological discovery and therapeutic development. *Trends in biochemical sciences*, *45*(12), 1080-1093.

[64] Benvenuto, M., Albonici, L., Focaccetti, C., Ciuffa, S., Fazi, S., Cifaldi, L., ... & Bei, R. (2020). Polyphenol-mediated autophagy in cancer: evidence of in vitro and in vivo studies. *International Journal of Molecular Sciences*, *21*(18), 6635.

[65] Luo, M., Ye, L., Chang, R., Ye, Y., Zhang, Z., Liu, C., ... & Han, L. (2022). Multi-omics characterization of autophagy-related molecular features for therapeutic targeting of autophagy. *Nature Communications*, *13*(1), 6345.

[66] López-Méndez, T. B., Sánchez-Álvarez, M., Trionfetti, F., Pedraz, J. L., Tripodi, M., Cordani, M., ... & González-Valdivieso, J. (2023). Nanomedicine for autophagy modulation in cancer therapy: a clinical perspective. *Cell & bioscience*, *13*(1), 44.

[67] Zheng, H., Hu, B., Sun, Q., Cao, J., & Liu, F. (2019). Applying a chemical structure teaching method in the pharmaceutical analysis curriculum to improve student engagement and learning. *Journal of Chemical Education*, *97*(2), 421-426.

[68] Nahar, L., & Sarker, S. D. (2019). *Chemistry for pharmacy students: general, organic and natural product chemistry*. John Wiley & Sons.