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Natural chromones targeting autophagy signalling pathways as potential anticancer interventions: a systematic review

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ABSTRACT

Chromones, a class of natural product-based compounds, have garnered considerable interest due to their potential anticancer properties, particularly through the modulation of autophagy. Autophagy is a cellular process involved in both cancer progression and suppression, making it a promising therapeutic target. This systematic review aimed to evaluate the role of chromone-based compounds in regulating autophagy for cancer treatment. A comprehensive search from 2004 to early 2024 yielded 568 records, from which 44 eligible studies were selected based on defined inclusion criteria. These studies collectively investigated 23 distinct phytochemicals, including isoflavones, biflavonoids, prenylated flavones, flavone glycosides, and flavones, providing a robust dataset for evaluating the role of chromones in autophagy modulation. Most compounds activated autophagy, leading to cancer cell death, while a minority triggered autophagic activation with cytoprotective effects. Mechanistically, these compounds primarily inhibited the PI3K/AKT/mTOR pathway, a key regulator of autophagy initiation. This inhibition resulted in increased expression of LC3-II and Beclin-1, which are involved in autophagosome formation, and a decrease in p62 levels, a marker of autophagic degradation. Although the findings demonstrate a strong link between natural chromones and autophagy activation, none of the compounds were found to inhibit autophagy as a means to promote cancer cell death. This strategy, however, has been reported for synthetic derivatives. These results highlight the potential of chromones as anticancer agents and support future research into designing analogues that can selectively activate or inhibit autophagy depending on therapeutic needs.

1. Introduction

Cancer is defined as the abnormal and aggressive growth of cells [1], with more than 200 types identified, most of which are classified based on the tissue of origin [2]. The global burden of cancer continues to increase, with significant disparities in incidence and mortality based on geographical, demographic, and socio-economic factors [3]. According to the World Health Organization (WHO), cancer was responsible for

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nearly 10 million deaths in 2020. In the United States alone, cancer mortality declined by 32 % between 1991 and 2019, preventing an estimated 3.5 million deaths [4]. Despite this, cancer remains the second leading cause of death after cardiovascular disease [5], with 2,041,910 new cases and 618,120 deaths projected for 2025 [6]. These statistics highlight the urgent need for more effective and less toxic cancer therapies. Conventional treatments such as chemotherapy and radiation therapy often result in severe side effects [7], prompting a shift in drug discovery towards safer, targeted therapies. Natural products have long served as a foundation for anticancer drug development, due to their chemical diversity and pharmacological relevance [8,9]. Many of these compounds, isolated from plants, microbes, and marine organisms, have demonstrated therapeutic efficacy and continue to inspire new drug leads [10].

Chromones, an important class of natural product-based compounds with a benzoannelated-pyrone ring, are widely distributed in numerous plant genera, including *Polygonum*, *Citrus*, *Hypericum*, *Cassia*, *Aloe*, and *Aquilaria*, and to a lesser extent, in genera of fungi, such as *Penicillium*, *Aspergillus*, and *Orbiocrella* [11]. The core structure, as illustrated in Fig. 1, is highly regarded in drug development due to its chemical stability, synthetic accessibility and capacity for diverse functional modification [12,13]. The biological activity of chromone derivatives is strongly influenced by their substitution patterns [14], enabling a wide range of pharmacological effects, including anticancer activity [15]. Chromone-based compounds have demonstrated therapeutic potential across numerous cancer types by modulating key molecular pathways. Mechanisms of action include mitochondria-activated apoptosis [16], downregulation of the MAPK [17] and PI3K/Akt/mTOR pathways [18], modulation of B-cell lymphoma 2 (Bcl-2) families [13], inhibition of DNA-PKcs and CDKs [19], and activation of caspases and poly (ADP-ribose) polymerase (PARP) [20]. Clinically relevant examples include P-276-00 (Riviciclib®) [21] and flavopiridol (Alvocidib®) [22], chromone derivatives currently in trials for cancers such as leukaemia and lymphoma [23].

In addition to these effects, recent studies have highlighted the role of chromones in regulating autophagy, a cellular process involved in cancer progression and response to therapy [24,25]. Compounds such as flavones and isoflavones have been shown to influence autophagy-related pathways, suggesting a promising therapeutic avenue [26–28]. While natural products have long served as a foundation for anticancer drug discovery, the specific role of chromone scaffolds in autophagy modulation remains underexplored [29]. Therefore, this systematic review aims to evaluate chromone-based compounds that modulate the autophagy signalling pathway in cancer models. While prior reviews have discussed the anticancer properties of chromones more broadly, none have systematically focused on their autophagy-regulating effects [15,30]. This review addresses that gap by assessing the mechanisms and therapeutic relevance of chromones in autophagy regulation, with the goal of informing future drug development efforts.

2. Autophagy and its role in cancer

Autophagy is a self-decomposition or intracellular recycling mechanism that generates the energy and macromolecular building blocks necessary to meet metabolic demands, maintain homeostasis, and facilitate the turnover of cellular components [31,32]. Ensuring the preservation of cell metabolism and energy balance, defending cells against damaged proteins, promoting cell survival, and safeguarding cell organelles from toxins are crucial for all cells [33]. Numerous autophagy-related proteins participate in initiating autophagy, forming pre-autophagy structures (PAS) and nucleating, elongating, and maturing autophagosomes. It also engages in autophagosome and lysosome fusion, as well as the breakdown of autophagic lysosomal content. The Unc-51-like autophagy activating kinase 1 (ULK1) complex, autophagy-specific class III phosphatidylinositol 3-kinase (PI3K) complex, ATG9A trafficking system, microtubule-associated protein 1A/1B-light chain 3 (LC3), and ATG12 ubiquitin-like conjugation systems are among the proteins involved in the autophagy process [34].

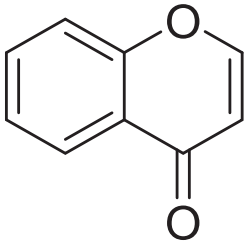


Fig. 1. Chemical structure of chromone core.

Autophagy is crucial for maintaining good health and preventing the development of diseases. Several health issues, including cancer, are associated with abnormal autophagy [35]. Thus, an effective approach for cancer treatment may target autophagy. However, autophagy plays a dual role in various cancer settings and stages, both promoting and suppressing tumour growth, as depicted in Fig. 2, which illustrates this context-dependent behaviour. Therefore, targeting autophagy in cancer therapy remains unclear [36]. Autophagy promotes tumour growth by supplying the metabolic demands of growing cancer cells *via* lysosomal degradation and recycling of proteins and organelles [37]. Thus, it plays a role in promoting the growth and survival of cancer cells, particularly under stress conditions such as nutrient deprivation or exposure to chemotherapy. This supportive role of autophagy in cell survival can also decrease the chances of apoptosis, as the autophagic process assists in preserving the overall cell well-being [38]. Based on a comprehensive review by Shin, several marketed drugs that act as autophagy inhibitors have been identified as potential therapeutic agents capable of reducing cancer cell survival, including bafilomycin A1, chloroquine, hydroxychloroquine, quinacrine, obatoclax, bortezomib, and thymoquinone [39].

Conversely, autophagy exerts a tumour-suppressive effect by preventing genomic instability and inducing apoptosis [40]. Autophagy plays a pivotal role in maintaining cellular homeostasis by eliminating damaged proteins and organelles, thereby mitigating the genomic instability that can initiate cancer [41]. Autophagy can also induce programmed cell death, preventing the survival and proliferation of damaged or mutated cells that can become cancerous [38]. Several autophagy promoters have been identified as potential therapeutic agents that can enhance cancer cell death by stimulating autophagic activity, thereby contributing to the elimination of cancerous cells. These include rapamycin, everolimus, metformin, perifosine, imbrutinib, magnolin, resveratrol, and spermidine [39].

Autophagy plays a multifaceted and context-dependent role in the development of cancer. It can support early cancer development and aid established cancer cells; however, it can also act as a safeguard mechanism to prevent or limit cancer progression by maintaining cellular health and promoting cell death when needed. For example, autophagy protects normal cells from malignant mutations and damaging stimuli during the early stages of cancer under normal conditions. In contrast, autophagy promotes and fuels tumour growth in late-stage and progressive cancers [42]. Moreover, autophagy suppresses tumour growth in early-stage cancer by destroying potentially oncogenic molecules. However, it also promotes tumour growth in late-stage cancer by reducing the microenvironmental stress [43]. The tumour microenvironment is nutrient- and oxygen-deficient, owing to inadequate vascularization in solid tumors and increased metabolic demand in actively growing cancer cells. Consequently, autophagy is induced for metabolic adaptation [43,44]. Thus, modulating autophagy, either by stimulating autophagic cell death or suppressing cytoprotective autophagy, depending on the specific context and stage of cancer, offers a promising approach for effectively targeting and combating this complex process in cancer development. A nuanced understanding of the dual nature of

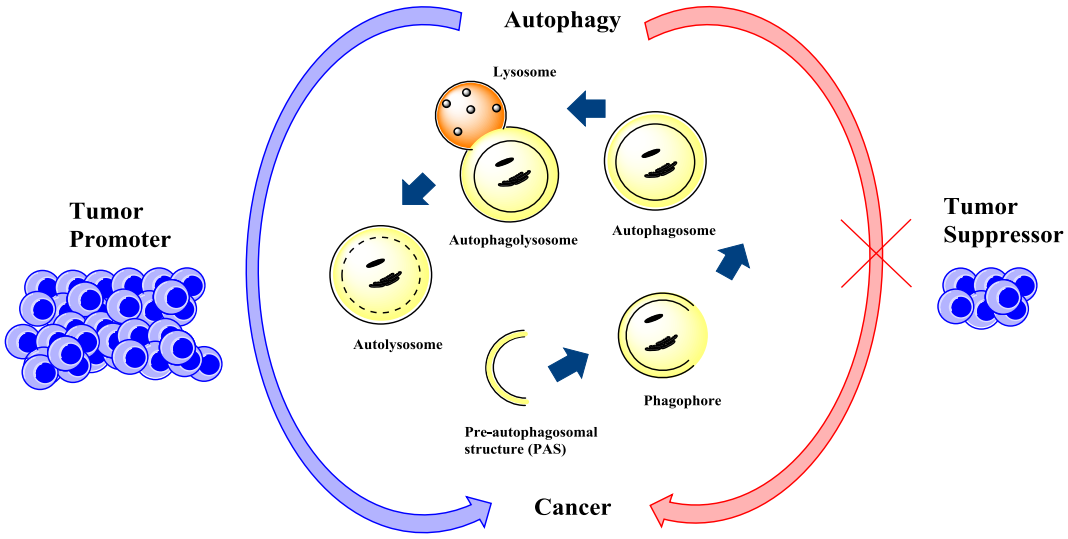


Fig. 2. Dual role of autophagy in cancer, indicating its tumour-suppressive and tumour-promoting potential.

autophagy is crucial for developing innovative cancer therapies.

3. Methodology

3.1. Literature search strategy

A systematic literature search was conducted using PubMed, Scopus, and Taylor & Francis databases. The search covered publications from January 2004 to January 2024. The search strategy was based on three main domains: chromone-based compounds, autophagy, and cancer therapy. A combination of keywords and synonyms was used, including: ("chromone-based" OR "chromone" OR "flavone" OR "isoflavone") AND ("autophagy") AND ("cancer therapy" OR "anticancer"). Boolean operators "OR" was used to connect words within the same domain, and "AND" was used to connect the primary search domains. Database-specific filters, such as original text, no more than 20 years of publication, and full text, were used for every database during the search.

3.2. Eligibility criteria

Only full-text original research published in English that focused on chromone-based compounds targeting autophagy in cancer cells were included in this review. Studies were excluded if they did not involve chromone-based compounds, did not investigate autophagy as a mechanism, or were unrelated to cancer cell models. Additionally, review articles, retracted publications, and non-retrievable records were excluded from consideration.

3.3. Study selection

After the literature search, the Mendeley Reference Manager was used to compile and upload all identified citations and delete duplicate records. Citation data of potentially relevant articles were exported from Mendeley into Excel to facilitate the screening process. The literature screening was conducted by two independent reviewers. Titles and abstracts were evaluated based on predefined inclusion criteria to ensure objectivity and consistency. The systematic review recorded and documented justifications for excluding full-text articles that matched the inclusion requirements. In addition, in cases of disagreement, the reviewers resolved conflicts through discussion and mutual consensus. A flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) was used to summarize the search results and inclusion process.

3.4. Data extraction

For data extraction, a predesigned data extraction tool was developed to retrieve relevant information from the selected articles systematically. The tool was designed to capture essential details, including the compound name, structure, source, cytotoxic concentration, type of cancer cell, cell line, treatment concentration, and autophagy-related mechanism of action. To ensure the reliability and consistency of the data extraction, the tool was piloted on a subset of articles and reviewed for clarity and completeness. Any discrepancies or ambiguities in the data were resolved through discussion between two independent reviewers, ensuring that all relevant information was accurately captured and documented. This process is essential for maintaining the robustness and reproducibility of the review findings. All retrieved data are displayed in figures and tables that comply with PRISMA standards [45]. The overall quality of the review and reported data was guaranteed by adhering to the PRISMA 2020 checklist [46].

4. Results

4.1. Literature search

A total of 568 studies were initially retrieved from three databases: 81 from Scopus, 324 from PubMed, and 163 from Taylor and Francis, which are potentially related to this study. After removing 59 duplicate records, 509 titles and abstracts were screened for relevance. Based on title and abstract screening, only 79 of the 509 available records were deemed eligible and advanced to the next round of full-text eligibility screening. Following this, 35 full-text articles were excluded for various reasons: 8 were review articles, 3 were retracted, 2 articles could not be retrieved, 3 did not involve chromone-based compounds, 14 did not investigate autophagy, and 5 were unrelated to cancer cells. As shown in Fig. 3, 44 articles fulfilled the inclusion criteria of this systematic review.

4.2. Studies characteristics

During the search phase, time limits were applied in this systematic review, and only articles published from 2004 onwards were accepted. Therefore, all the 44 selected articles were published between 2012 and 2021. Table 1 lists all 23 chromone-based compounds that regulate autophagy signalling pathways in cancer cells from the 44 selected studies. The chromone-based compounds were separated into five groups: isoflavones, biflavonoids, prenylated flavones, flavone glycosides, and flavones. Additionally, among the 23 compounds examined,

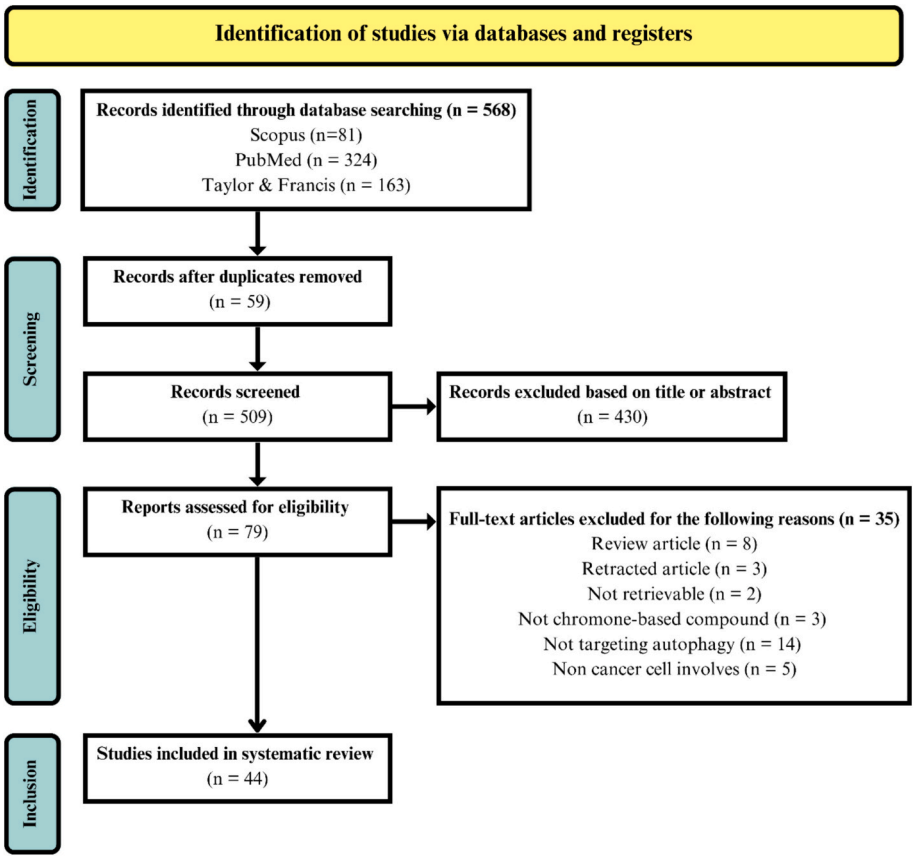


Fig. 3. The PRISMA flow diagram illustrates the article-selection process.

only one compound, compound **11**, was derived from a natural product (referred to as a natural product derivative, NPD), whereas the remaining compounds were isolated directly from natural sources (referred to as natural product isolations, NPIs). These chromone-based compounds have demonstrated various targets in the autophagy signalling pathway to prevent cancer cell proliferation. PI3K/ protein kinase B (AKT)/ mammalian target of rapamycin (mTOR) is a crucial autophagy pathway, in which several compounds stimulate autophagy by disrupting the pathway [27,47,48].

4.3. Autophagy-related mechanisms involving chromone-based compounds

In Table 2, the autophagy-related mechanisms of chromone-based compounds are summarized, along with the concentration treatment, type of cell line, and cancer involved. The cytotoxicity concentrations of the compounds were also included to demonstrate that all chromone-based compounds investigated in the selected studies exhibited anticancer properties, reaffirming their potential as a structural foundation for the development and advancement of novel anticancer drugs. The data showed that various autophagy-related proteins modulate the autophagy pathway in cancer cells, including the ULK1 complex, ATG9A trafficking system, PI3K complex, LC3, and ATG12 ubiquitin-like conjugation system. Additionally, autophagic protein expression levels of LC3-II, Beclin-1, and p62 were used as biomarkers to indicate that the compound could induce autophagy in treated cells [47,49,50].

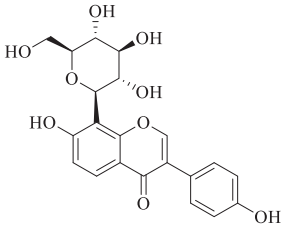
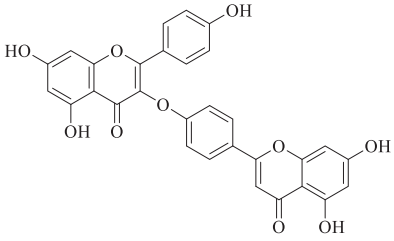
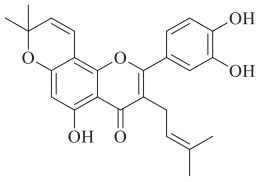
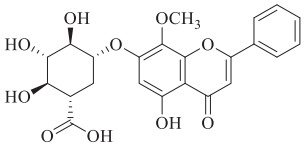
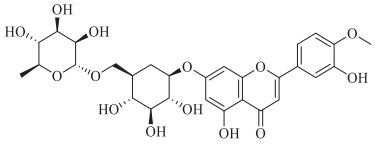
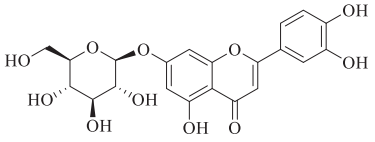
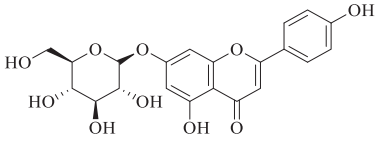
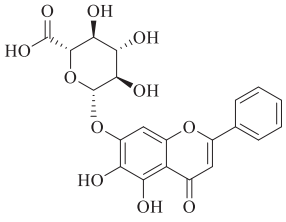
Moreover, not all compounds hinder the growth of cancerous cells by inducing autophagy, which serves both cytotoxic and cytoprotective functions [36]. Certain chromone-based compounds exhibit dual functionality in modulating autophagy, capable of inducing either cytotoxic autophagy or triggering cytoprotective autophagy through their influence on distinct autophagy pathways. Notably, compounds within the flavone group, specifically compounds **17–19** and **21–24**, exhibited this dual role in autophagy regulation, with their effects dependent on the specific cancer cells involved. Small interfering RNA (siRNA) and autophagy inhibitors, including 3-methyladenine (3-MA), chloroquine (CQ), hydroxychloroquine (HCQ), and bafilomycin A1 (Baf A1), have been used to investigate the role of autophagy in cell death [47,51–53]. From the tabulated data, the antiproliferative effect of chromone-based compounds depends on the regulation of autophagy, either by inhibiting or inducing autophagy, which can lead to cell death. Hence, the selected studies provided substantial evidence supporting the effectiveness of chromone-based compounds in modulating autophagy for cancer treatment.

5. Discussion

Before discussing the results of this systematic review, it is essential to examine the complex relationship between the mTOR signalling pathway and critical autophagy-related genes (ATG) that jointly control the autophagic response in mammalian cells (Fig. 4). This introductory analysis is crucial for establishing the necessary context for an in-depth exploration of the highlighted studies on chromone-based compounds that target autophagy in cancer therapy.

The ULK1 kinase complex, which consists of FAK family interacting proteins of 200 kDa (FIP200), ULK1/2, ATG101, and ATG13, is one of the key proteins involved in autophagy. The ULK1 kinase complex oversees aberrant cell signal detection, autophagy initiation, ATG protein recruitment to PAS, and autophagosome regulation [54]. Autophagy can be activated in response to reactive oxygen species (ROS) or cellular stress such as genome instability and nutrient deprivation. Autophagy is promoted by the upregulation of 5′ adenosine monophosphate-activated protein kinase (AMPK), which inhibits mTORC1 to supply cells with energy and nutrients [55]. In mammals,

Table 1
Chemical structures and sources of chromone-based compounds that target autophagy in cancer cells.

Group of compounds	No. of compound	Compound	Structure	Source	References
Isoflavone	1	Puerarin		*Radix Puerariae*	[73]
Biflavonoid	2	Delicaflavone		*Selaginella doederleinii*	[27]
Prenylated flavone	3	Morusin		*Morus alba*	[51]
Flavone glycoside	4	Wogonoside		*Scutellaria baicalensis* Georgi	[47]
	5	Diosmin		Citrus fruits	[77]
	6	Luteoloside		*Gentiana macrophylla*	[78]
	7	Apigetrin		Various fruits and vegetables	[50]
	8	Baicalin		*Scutellaria baicalensis*	[79,82]

(*continued on next page*)

Table 1 (*continued*)

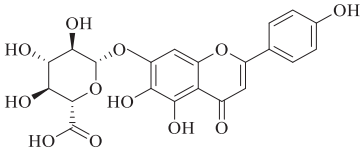
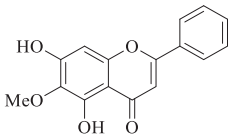
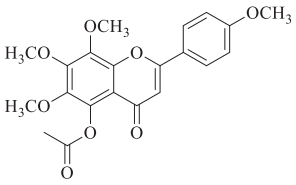
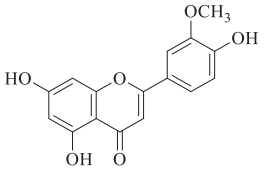
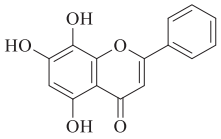
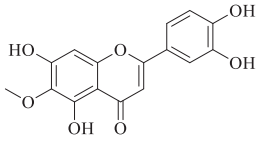
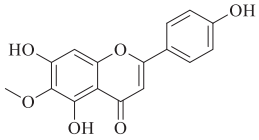
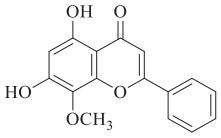
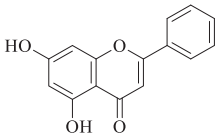
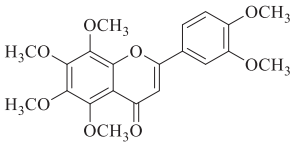
Group of compounds	No. of compound	Compound	Structure	Source	References
	9	Scutellarin		*Erigeron breviscapus* (Vant.) Hand-Mazz	[52,83]
Flavone	10	Oroxylin A		*Scutellariae radix*	[85]
	11	5-acetyloxy-6,7,8,4′-tetramethoxyflavone		NPD (Tangeritin derivative)	[48]
	12	Chrysoeriol		Various plant kingdom	[49]
	13	Norwogonin		*Scutellaria baicalensis*	[87]
	14	Eupafolin		*Artemisia princeps*	[88]
	15	Hispidulin		*Salvia involucrate*	[89]
	16	Wogonin		*Scutellaria baicalensis*	[90,91]
	17	Chrysin		Various dietary sources	[92,93]
	18	Nobiletin		*Citrus depressa* Hayata	[94,95]

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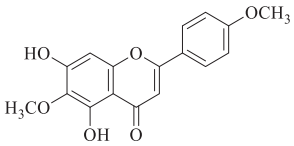
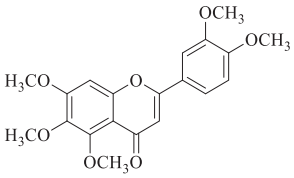
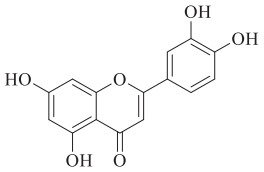
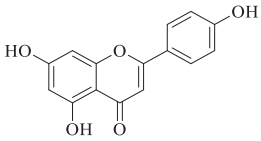
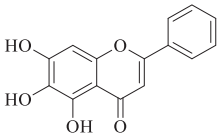
Table 1 (*continued*)

Group of compounds	No. of compound	Compound	Structure	Source	References
	19	Pectolinarigenin		*Chromolaena odorata*	[96,97]
	20	Sinensetin		*Orthosiphon stamineus*	[98,99]
	21	Luteolin		Various plants	[102–106]
	22	Apigenin		Various fruits and vegetables	[53,107–110]
	23	Baicalein		*Scutellaria baicalensis*	[27,111–115,123]

assembly of the ULK1 complex, which is controlled by mTORC1, is initially necessary to produce phagophores. Inhibition of mTORC1 dephosphorylates the ULK1 complex, causing it to become active and localize to the phagophore [56]. The PI3K complex is then activated in response to the activation of the ULK1 complex [57].

ATG14L, Beclin1, vacuolar protein sorting (VPS) 34, and VPS15 are components of the PI3K complex that control the size and amount of autophagosomes. Beclin-1 interacts with VPS34 to activate VPS34 kinase activity [58,59]. The Beclin-1-PI3K complex activation causes the isolation membrane to undergo nucleation [60]. The next protein involved was the ATG9A trafficking system, which includes ATG9A, ATG2A, and WIPI1/2. ATG9A/ATG9 phosphorylation is essential for WIPI1/2/ATG18 and LC3/ATG8 recruitment, with ULK/ATG1 possessing the ability to phosphorylate ATG9A/ATG9 [61]. Additionally, ATG12 ubiquitin-like conjugation systems, comprising ATG5, ATG7, ATG10, ATG12, and ATG16L1, significantly contribute to the autophagy process. ATG12 is conjugated to ATG5 by ATG10 after ATG7 activates ATG12. As a result of ATG16L protein stabilising the conjugate, the ATG12-ATG5-ATG16L complex is generated, establishing the LC3-conjugated system [62–65]. The LC3-conjugated system is engaged in the elongation process to form autophagosomes and functions as a biomarker to denote the presence of autophagy [65–67]. Autolysosomes are created at the end of the autophagy process when lysosomes fuse with fully developed autophagosomes to degrade and recycle damaged proteins and organelles [68].

In addition, autophagy receptor sequestosome 1 (SQSTM1), p62, lysosomes, and LC3 markers are predicted to co-localize in cells undergoing autophagy, and immunofluorescence microscopy may be used to identify them in individual cells selectively [69]. p62 is a frequently used marker of autophagic flux, because its levels decrease when autophagy is activated and increase when it is inhibited [70]. p62 plays various roles in autophagy, including acting as a cargo receptor for ubiquitinated targets and delivering them to autophagosomes for destruction. It may also activate mTORC1 in lysosomes and contain an LC3-interacting domain [71]. The increase in p62 levels may indicate ineffective autophagy; therefore, it is a popular marker of autophagy flux [72].

Building on an exploration of the complex mechanisms regulating autophagy and its key regulators, this systematic review focuses on the specific role of chromone-based compounds in targeting autophagy for cancer therapy. This is the first systematic review to investigate chromone-based compounds in the context of autophagy modulation in cancer treatment. A thorough literature search yielded 568 bibliographic articles. After applying the rigorous inclusion and exclusion criteria, 44 articles were selected and carefully reviewed. These studies examined various categories of chromone-based compounds and their mechanisms for modulating the autophagy signalling pathway in different cancer cell types. Among these, 23 distinct chromone-based compounds were identified, including isoflavones, biflavonoids, prenylated flavones, flavone glycosides, and flavones, each demonstrating unique effects on autophagy and inhibition of cancer cell growth. The PRISMA checklist was used to ensure high-quality reporting. However, this review had several limitations. First, only studies published in English were included, which may have excluded relevant studies published in other languages. Second, the review focused on articles published from 2004 onward to ensure inclusion of the most current and relevant information. Finally, some articles were excluded due to a lack of access to full texts or retraction, preventing their inclusion despite meeting the initial criteria.

Table 2
Cytotoxic effects of chromone-based compounds in cancer cells and their autophagy-related mechanisms of action.

Compound number	Cytotoxic concentration	Cancer types	Cell lines/ animal	Treatment concentration	Autophagy-related mechanism of action	Reference
Chromone-based compounds as stimulators of autophagic cell death						
1	5 μM	Non-small cell lung cancer (NSCLC)	NCI-H441	5, 10, 20 μM	• ↑ ATG5 and ↓ LC3-I • ⊥ of PI3K/AKT and ERK pathway	[73]
2	40 μg/mL	Lung cancer	A549 PC-9 Nude mice	10, 20, 40 μg/mL	• ↑ LC3-II • ⊥ of AKT/mTOR/p70S6K pathway • *In vivo*: ↑ LC3	[27]
3	IC_{50}, A549: 12.32 μM NCI–H292: 7.92 μM	NSCLC	A549 NCI–H292	10, 20, 30 μM	• ↑ LC3-II and ↓ SQSTM1/p62 • ROS generation • ↓ of AKT pathway and ⇢ of JNK, ERK pathway • ⊥ of autophagy and cell death by CQ co-administration	[51]
4	IC_{50}, U251MG: 193.44 μM U87MG: 199.83 μM	Glioblastoma	U251MG U87MG	250 μM	• ↑ LC3-II, Beclin-1And ↓ p62 • ⇢ of p38 MAPK signalling pathway • ⊥ of PI3K/AKT/mTOR/p70S6K pathway • Generation of ROS • ⊥ of autophagy by 3-MA, led to ↓ apoptosis and cell death	[47]
5	IC_{50}, MCF-7: 13.93 μM MDA-MB-231: 19.46 μM SK-BR-3: 17.92 μM	Breast cancer	MCF-7 MDA-MB-231 SK-BR-3	5, 10, 20 μM	• ⇢ of ERK • ↑ nitric oxide	[77]
6	IC_{50}, A549: 62.19 μM H292: 45.78 μM	NSCLC	A549 H292	60 M	• ↑ LC3B-II, Beclin-1And ↓ p62 • ⊥ of ROS-mediated AKT/mTOR/p70S6K pathway • ⊥ of autophagy by 3-MA, led to ↑ cell viability	[78]
7	IC_{50}: 52.13 μM	Gastric cancer	AGS	25, 50, 100 μM	• ↑ LC3B-II, p62, Beclin-1 • ↓ of PI3K/AKT/mTOR pathway • ↑ of IRE1α/JNK/p62 pathway	[50]
8	IC_{50}: 40 μM	Human hepatocellular carcinoma	SMMC-7721	40, 80, 160 μM	• ↑ Beclin-1 • ↓ of CD147 • ⊥ of autophagy by 3-MA impeded cell death	[79]
	IC_{50}: 300 μM	Glioblastoma	U87 U251	25, 50, 100, 200, 300 μM	• ↑ Beclin-1And ↓ p62 • ↓ AKT and mTOR phosphorylation • Intracellular Ca^{2+} overload • ⊥ of autophagy by 3-MA suppressed apoptosis: ↓ LC3B-II, ↓ BAX, and ↑ Bcl-xL	[82]
9	IC_{50}, A549: 0.43 μg/mL A549/DDP: 16.07 μg/mL	NSCLC	A549 A549/DDP Nude mice	120 μM	• ↑ LC3-II • ↑ autophagy induced by cisplatin *via* ↓ c-Met/AKT pathway • ⊥ of autophagy by HCQ contributed to cisplatin resistance • *In vivo*: combination with cisplatin ↑ LC3-II, ↓ phosphorylated AKT and c-Met	[83]
	40 μM	NSCLC	PC-9 H1975 Nude mice	40, 80, 160 μM	• ↑ LC3-II • ⇢ of ERK1/2 • ⊥ of AKT signalling pathway • ⊥ of autophagy by HCQ, led to ↓ apoptosis and antiproliferative ability • *In vivo*: ↑ LC3-II, phosphorylated ERK1/2 level, and ↓ phosphorylated AKT	[52]
10	IC_{50}: 59.48 μM	Hepatocellular carcinoma	HepG2	80 μM	• ↑ Beclin-1, LC3-II • ⊥ of mTOR pathway • ⊥ of autophagy by 3-MA suppressed apoptosis: ↓ caspase-3, cleaved-PARP	[85]
11	IC_{50}: 3.2 μM	NSCLC	CL1–5 Nude mice	2.5, 5 μM	• ↑ LC3-II • ⊥ of PI3K/AKT/mTOR pathway • *In vivo*: LC3-II ↑ • ⊥ of autophagy by 3-MA suppressed apoptosis: ↓ LC3-II, ↓ PARP	[48]
12	IC_{50}: 15 μM	Lung cancer	A549	7.5, 15, 30 μM	• ↑ LC3-II, Beclin-1And ↓ p62 • ⊥ of mTOR/PI3K/AKT signalling pathway	[49]
13	IC_{50}: 15.5 μM	Colon cancer	SW48	7.5, 15, 30 μM	• ↑ LC3-II	[87]
14	IC_{50}: 5.06 μM	B-cell non-Hodgkin lymphoma	OCI-LY-3	2, 4, 8 μM	• ↑ Beclin-1And ↓ p62 • ↓ of AKT/mTOR/P70S6K signalling pathway • ⊥ of autophagy by 3-MA suppressed apoptosis: ↓ LC3-II, ↓ cleaved-PARP	[88]
15	10 μM	Prostate cancer	Du145 VCaP Nude mice	10, 50 μM	• ↑ LC3-II • ↓ phosphorylation of mTOR • ⇢ of PPARγ • *In vivo*: ⇢ of PPARγ	[89]
16	IC_{50}: 8 μM	Colorectal cancer	SW48	4, 8, 16 μM	• ↑ of LC3-II, Beclin-1 • ⊥ of PI3K/AKT and STAT3 signalling pathways	[90]
17	40 μM	Breast cancer	MCF-7	40, 80, 160 μM	• ↑ LC3-II	[92]

(*continued on next page*)

Table 2 (*continued*)

Compound number	Cytotoxic concentration	Cancer types	Cell lines/ animal	Treatment concentration	Autophagy-related mechanism of action	Reference
18	IC_{50}: 6.12 μM	Pancreatic cancer	MIAPaCa-2	6.12, 12.5, 25 μM	• ↑ LC3-II and ↓ p62	[94]
19	IC_{50}: 10 μM	Hepatocellular carcinoma	SK-HEP-1	5, 10, 20 μM	• ↑ LC3-II, Beclin-1And ↓ p62	[96]
	IC_{50}, AGS: 124.79 μM MKN28: 96.88 μM	Gastric cancer	AGS MKN28	50, 100 μM	• ↑ LC3-II, ↓ Beclin-1 • ↓ of PI3K/AKT/mTOR pathway	[97]
20	25 μM	Hepatocellular carcinoma	HepG2	50, 100 μM	• ↑ LC3B-II, Beclin-1And ↓ p62 • ↓ p53-mediated AMPK/mTOR signalling pathway • ⊥ of autophagy by 3-MA, led to ↑ cell viability	[98]
21	50 μM	Lung cancer	NC I- H4 60	200 μM.	• ↑ LC3-II • ⊥ of autophagy by Baf A1, led to ↓ apoptotic cell death	[102]
	IC_{50}: 34.24 μM	Hepatocellular Carcinoma	SMMC-7721	25, 50, 100 μM	• ↑ LC3B-II, Beclin-1 • ⊥ of autophagy by CQ ↓ apoptosis: ↓ caspase 8 and ↑ Bcl-2	[103]
22	12.5 μM	Papillary thyroid carcinoma	BCPAP	12.5, 25, 50 μM	• ↑ LC3-II, Beclin-1And ↓ p62 • ROS formation • ⊥ of autophagy by 3-MA led to ↑ cell viability: ↓ LC3-II and p62 degradation	[107]
	30 μM	Gastric cancer	AGS SNU-638	50 μM	• ↑ ATG 5, Beclin-1, LC3-II and ↓ p62 • ↓ mTOR phosphorylation and ↑ AMPKα and ULK1Activation • ⇢ of PERK signalling and ⊥ HIF-1α and EZH2 • Co-treatment with LC3B siRNA and ATG5 siRNA ↑ cell viability: ↓ LC3B and ATG5	[53]
	IC_{50}: 30 μM	Colon cancer	HT-29	15, 30, 60 μM	• ↑ Beclin-1, LC3-II and ↓ p62 • ⊥ of mTOR/PI3K/AKT signalling pathway	[108]
	IC_{50}: 45.55 μM	Endometrial adenocarcinoma	Ishikawa cells	20, 40, 60, 80, 100, 120, 140, 160 μM	• ↓ AMPK, mTOR, P70S6K, and ATG4 • ↑ ULK1, Beclin 1, LC3B, ATG5, and ATG13 • ⊥ of autophagy by CQ increased colony formation	[124]
23	IC_{50}, MCF-7: 13.98 μM MDA-MB-231: 19.01 μM	Breast cancer	MCF-7 MDA-MB-231 Nude mice	10, 20, 40 μM	• ↑ Beclin-1, LC3B • ↓ of PI3K/AKT signalling pathway • *In vivo*: ↓ phosphorylated AKT, ↑ LC3	[111]
	2.5 μg/mL	Prostate cancer	PC-3 DU145	0.5, 1, 2.5, 5,10 μg/mL	• ↑ LC3B-II • ⇢ of AMPK/ULK1And ⊥ mTOR/Raptor expression	[112]
	10 μM	Glioma	U251	10, 20, 40, 80 μM	• ↑ LC3B-II, Beclin-1 • ⇢ of AMPK signalling pathway	[26]
	IC_{50}: 10 μM	Thyroid cancer	MDA-T68	10, 20, 40 μM	• ↑ LC3-II, Beclin-1 • ↑ NF-κB	[113]
	IC_{50}, SGC-7901/DDP: 244.50 μM SGC-7901: 146.50 μM	Gastric cancer	SGC-7901 SGC-7901/ DDP	12.5, 25, 50, 100, 200 μM	• ↑ LC3, Beclin-1 • ↓ of AKT/mTOR signalling pathway	[114]
Chromone-based compounds as inducers of cytoprotective autophagy						
16	50 μM	Nasopharyngeal carcinoma	NPC-TW076 NPC-TW039	50 μM	• ↑ LC3-II • ⊥ of mTOR/P70S6K pathway • ⊥ of autophagy by 3-MA promoted apoptosis	[91]
17	10 μM	Endometrial cancer	HEC-1A Ishikawa	10, 20, 40, 80 μM	• ↑ LC3-II, Beclin-1And ↓ p62 • ⊥ of ROS-mediated AKT/mTOR signalling pathway • ⊥ of autophagy by CQ led to ↓ cell proliferation and ↑ apoptosis	[93]
18	12.5 μM	Gastric cancer	SNU-16	12.5, 25, 50 μM	• ↓ phosphorylated AKT and mTOR • ↑ LC3-II and ↓ p62 • ⊥ of autophagy by CQ led to ↓ cell proliferation and ↑ apoptosis: ↑ cleaved PARP	[95]
20	IC_{50}: 135.4 μM	T-cell lymphoma	Jurkat	50, 100 μM	• ↑ LC3-II, Beclin-1And ↓ p62 • ⇢ of ROS/JNK • ⊥ of AKT/mTOR signalling pathway • ⊥ of autophagy by 3-MA led to ↓ cell viability and induced apoptosis	[99]
21	IC_{50}: 48.8 μM	Colon cancer	SW620	1, 2, 5, 10 μM	• ↑ LC3B-II, ATG7, Beclin-1 • ⊥ of autophagy by 3-MA led to ↓ cell viability	[105]
	2.5 μM	Hepatocellular carcinoma	Hep3B HepG2	5, 10 μM	• ↑ LC3-II and ↓ p62 • ⊥ of autophagy by 3-MA and CQ led to ↑ cell death	[104]
	IC_{50}, A172: 174.28 μM U-373MG: 236.09 μM	Glioblastoma	A172 U-373MG	25, 50, 100 μM	• ↑ LC3-II, p62 and ↓ ATG5, Beclin-1 • ⊥ of autophagy by 3-MA led to ↑ apoptosis: ↓ LC3, ↑ PARP cleavage	[106]
22	25 μM	Colon cancer	HCT116	6.25, 12.5, 25, 50 μM	• ↑ LC3-II • ⊥ of autophagy by 3-MA led to ↑ apoptosis: ↓ LC3-II, ↑ PARP cleavage and ↓ procaspase-3, -8 and -9	[109]
	10 μM	Hepatocellular carcinoma	HepG2 Nude mice	10, 20, 40 μM	• ↑ LC3-II, ATG5, Beclin-1 • ⊥ of PI3K/AKT/mTOR pathway • *In vivo*: ↑ LC3-II	[110]

(*continued on next page*)

Table 2 (*continued*)

Compound number	Cytotoxic concentration	Cancer types	Cell lines/ animal	Treatment concentration	Autophagy-related mechanism of action	Reference
					• ⊥ of autophagy by 3-MA led to ↑ apoptosis: ↓ LC3-II, ↑ cleaved-caspase-3, −9, cleaved-PARP and BAX while ↓ Bcl-2	
23	12.5 μM	Ovarian cancer	HEY	12.5, 25, 50 μM	• ↑ LC3-II, Beclin-1 • ⇢ of ERK • ⊥ of autophagy by CQ promoted apoptosis and ↓ cell viability: ↟ of cleaved-PARP	[115]
	25 μM	Oral squamous cell carcinoma	Cal27	25, 50, 100 μM	• ↑ LC3-II, Beclin-1And ↓ p62 • Generation of ROS • ⊥ autophagy by Baf A1 induced apoptotic cell death	[123]

Note: ↑ – increase; ↓ – decrease; ⇢ – activation; ⊥ – inhibition; ↟ – upregulation; ↡ – downregulation; IC_{50} – half maximal inhibitory concentration; Bcl-2-associated X protein (BAX); B-cell lymphoma-extra-large (Bcl-xL); B-cell lymphoma 2 (Bcl-2).

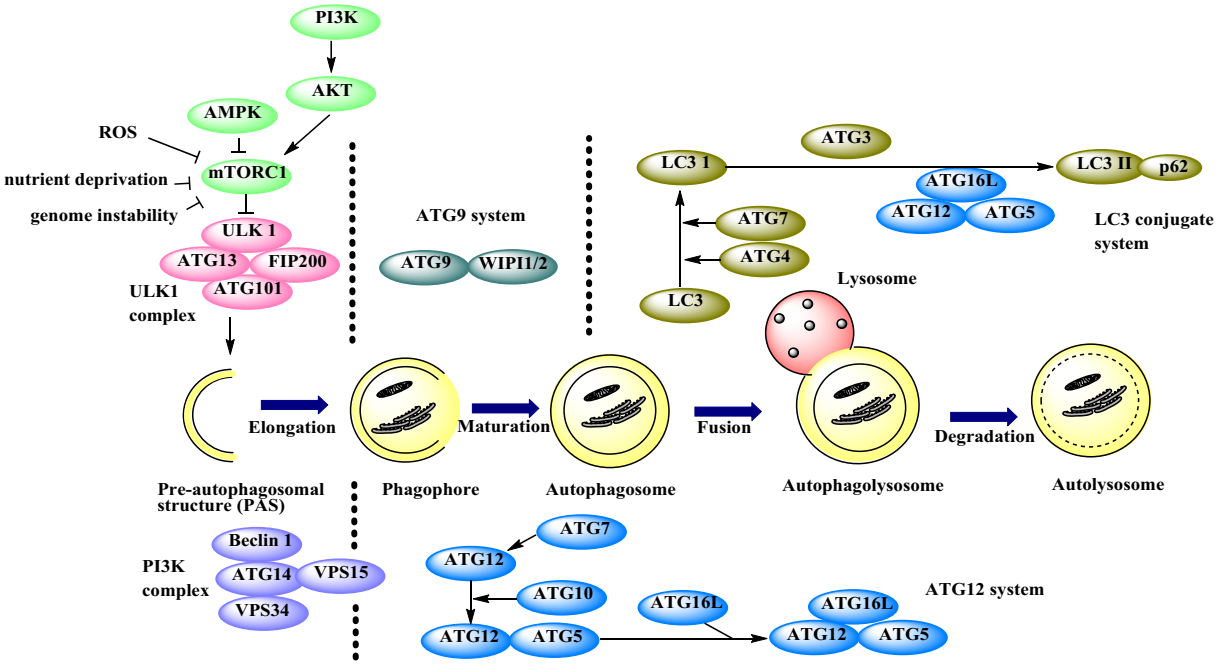


Fig. 4. The process of autophagy.

5.1. *Isoflavones targeted autophagy in cancer cells*

Out of the twenty-three compounds investigated, puerarin (compound **1**) was the only one classified as an isoflavone isolated from *Radix puerariae* (Kudzu roots). Puerarin (daidzein 8-C-glucoside) has been shown to exhibit anticancer activity in various types of cancer. Hu et al. (2018) observed that puerarin significantly inhibited the growth of non-small cell lung cancer (NSCLC) cell lines by promoting cell apoptosis and upregulating the expression levels of proteins involved in the mitochondrial-mediated apoptosis pathway. Puerarin also demonstrated time- and dose-dependent abilities to reduce the viability of NCI-H441 human lung adenocarcinoma cell lines. It also exhibited the ability to slightly induce cell autophagy through the PI3K/Akt and MAPK/Erk1/2 signalling pathways. It has been suggested that puerarin may induce autophagy in NCI-H441 cells, leading to a decrease in LC3-I and an increase in ATG5 protein levels. Notably, the level of LC3-II, which is associated with the extent of autophagosome formation, did not differ noticeably from that in the control. As suggested by researchers, this may be because the early phases of autophagy were present in the samples used in this investigation. Additionally, puerarin treatment dose-dependently reduced the phosphorylation levels of extracellular signal-regulated kinase (ERK) and AKT, promoting NCI-H441 cell autophagy by inhibiting the PI3K/AKT and ERK signalling pathways [73]. Thus, puerarin shows promise as an anticancer therapy for treating NSCLC, as it can limit cell proliferation by inducing cytotoxic autophagy.

5.2. *Biflavonoids targeted autophagy in cancer cells*

Delicaflavone (compound **2**), a rare biflavonoid found in *Selaginella doederleinii*, induces cytotoxic autophagy, as demonstrated by *in vitro* and *in vivo* tests [27,74]. When administered at doses exceeding 40 μg/mL, delicaflavone caused dose- and time-dependent reductions in the survival of PC-9 and A549 cells. Delicaflavone demonstrated time- and dose-dependent increase in LC3-II levels, indicating autophagic cell death. Additionally, delicaflavone induced autophagy in the respective cell lines by modulating distinct signalling pathways. It induces autophagy by blocking the AKT/mTOR/70-kDa ribosomal protein S6 kinase (p70S6K) pathway, resulting in time- and dose-dependent reductions in the phosphorylation of AKT, mTOR, and p70S6K [27]. These findings suggest that delicaflavone has potential as a therapeutic agent for anticancer treatment, particularly in the context of lung cancer, where autophagy is the key mechanism of action.

5.3. Prenylated flavones targeted autophagy in cancer cells

Morusin (compound **3**) is a naturally occurring prenylated flavonoid found in *Morus alba* root bark [51]. Morusin dose- and time-dependently impeded the proliferation of NCI-H292 and A549 cells, with IC_{50} values of 7.92 and 12.32 μM, respectively. After 0.5 h of morusin treatment, both cell lines exhibited a dose-dependent increase in LC3-II and a reduction in SQSTM1/p62 levels, indicating the occurrence of autophagy. Furthermore, the induction of autophagy by morusin was confirmed to contribute to enhanced cell death, as evidenced by co-treatment with CQ, a well-known autophagic flux inhibitor. This co-treatment effectively reversed the impairment in cell viability. The PI3K/AKT, ERK, and JNK pathways, which belong to the mitogen-activated protein kinase (MAPK) group, are essential regulators of cell growth, proliferation, and apoptosis [75,76]. The proposed mode of action by which morusin triggered autophagy in NCI-H292 and A549 cells involved the suppression of PI3K/AKT and the activation of the JNK and ERK pathways, characterized by a decrease in AKT phosphorylation and an increase in JNK and ERK phosphorylation. Morusin exhibited a pro-autophagic effect by decreasing the level of SQSTM1/p62 and increasing the level of LC3-II.

Furthermore, morusin administration led to a significant increase in ROS production. When co-administered with the ROS scavenger *N*-acetyl-L-cysteine (NAC), induced autophagy was reversed, implying that ROS plays a pivotal role in autophagy activation. Furthermore, combined treatment with morusin and NAC diminished the capacity of morusin to enhance JNK or ERK phosphorylation while reducing AKT phosphorylation, suggesting that the elevation of ROS levels by morusin likely contributed to AKT inhibition and the activation of JNK and ERK [51]. Consequently, further research on morusin is warranted, as it shows promise as a potential therapeutic agent for lung cancer.

5.4. Flavone glycosides targeted autophagy in cancer cells

Six flavone glycosides, wogonoside (**4**), diosmin (**5**), luteoloside (**6**), apigetrin (**7**), baicalin (**8**), and scutellarin (**9**), have been shown to induce cytotoxic autophagy and may be used to treat cancer. These compounds exhibited significant concentration- and time-dependent inhibition of cell growth, with IC_{50} values ranging from 13.93 to 300 μM across various cancer cell lines (Table 2).

Wogonoside (**4**), isolated from *Scutellaria baicalensis* root, exhibits cytotoxic effects in human glioblastoma cells [47]. It induces cellular autophagy by increasing LC3 dots, autophagy-related protein levels, and changes in cellular morphology. Wogonoside also increased autophagic flux by enhancing the formation of acidic vesicular organelles (AVOs) and increasing LC3 turnover and p62 degradation. Wogonoside-induced autophagy and apoptosis involve the participation of ROS, PI3K/AKT/mTOR/p70S6K signalling pathway, and p38 MAPK signalling pathway. These results support the use of wogonoside as a candidate treatment for human malignant gliomas.

Diosmin (**5**) is widely distributed in citrus fruit. At low concentrations (5 and 10 μM), it exhibited anticancer effects in MCF-7 cells by increasing the levels of p53, p21, and p27, inducing stress-induced premature senescence, and causing G2/M cell cycle arrest. Diosmin stimulates changes in global DNA methylation patterns, DNA damage, and nitrosative stress. The compound induced autophagy in MCF-7, MDA-MB-231, and SK-BR-3 cells, while also maintaining steady-state levels of phosphorylated ERK1/2 and the status of p53. These findings suggest that diosmin is a promising candidate for breast cancer therapy [77].

Luteoloside (**6**), found in *Gentiana macrophylla*, induced G0/G1 phase arrest associated with reduced expression of CyclinE, CyclinD1And CDK4 and inhibited cell proliferation in NSCLC cells [78]. It induces autophagy in lung cancer cells, which correlates with the overexpression of LC3-II, Beclin-1, the breakdown of p62, and the formation of autophagic vacuoles. When lung cancer cells were treated with luteoloside, autophagy was induced by the inhibition of the PI3K/AKT/mTOR/p70S6K pathway, as evidenced by the downregulation of p-mTOR, p-Akt (Ser473), and p-p70S6K (Thr389). Luteoloside-induced autophagy was correlated with ROS production. These findings support luteoloside as a potential anti-cancer agent for targeting NSCLC through the inhibition of proliferation, PI3K/AKT/mTOR/p70S6K signalling, and induction of autophagy.

Apigetrin (**7**), widely distributed in various fruits and vegetables, has been shown to induce autophagy in gastric cancer cells, specifically AGS cells, as evidenced by the upregulation of autophagy-related markers, including LC3B-II, p62, and Beclin-1 [50]. Notably, apigetrin significantly suppressed mTOR, PI3K, and AKT phosphorylation, indicating its role in promoting autophagy through the inhibition of the PI3K/AKT/mTOR signalling pathway. Furthermore, treatment with apigetrin led to upregulation of inositol-requiring enzyme 1α (IRE1α)/JNK/p62 protein expression in AGS cells, suggesting that apigetrin induces autophagic cell death *via* endoplasmic reticulum stress in gastric cancer cells. This phenomenon is associated with activation of the stress-induced JNK pathway by IRE1α in endoplasmic reticulum-stressed cells. Together, these results highlighted the anticancer properties of apigetrin by stimulating autophagy and cell death specifically in gastric cancer cells.

Baicalin (**8**), derived from the roots of *Scutellaria baicalensis,* was investigated for its effects on human hepatocellular carcinoma cells, specifically SMMC-7721 cells. Treatment with baicalin resulted in increased levels of Beclin-1, indicating the induction of autophagy. Moreover, a significant downregulation of CD147 expression was observed in SMMC-7721 cells treated with baicalin, suggesting that the induction of autophagy by baicalin may be mediated through the downregulation of CD147 expression [79]. Previous studies have shown that cluster of differentiation 147 (CD147) inhibits autophagy and autophagic cell death in human hepatocellular carcinoma cells [80,81].

Baicalin was also evaluated against glioblastoma cells, including U251And U87 cells, where it exhibited an increase in Beclin-1 expression while concurrently reducing levels of p62. Furthermore, baicalin inhibited mTOR and AKT phosphorylation, promoting autophagy *via* the inhibition of the AKT/mTOR signalling pathway. Autophagy induction by baicalin in U251And U87 cells was found to be facilitated by intercellular calcium overload, suggesting that calcium overload might activate the AMPK/mTOR pathway [82]. The induction of autophagy by baicalin was confirmed in both SMMC-7721 cells and glioblastoma cells using the autophagy inhibitor 3-MA, as evidenced by their ability to counteract autophagy induced by baicalin-mediated cell death. These findings underscore the anticancer potential of baicalein, demonstrating its ability to induce autophagy and inhibit cell growth in hepatocellular carcinoma and glioblastoma cells.

Scutellarin (**9**), derived from *Erigeron breviscapus* (Vant.) Hand-Mazz or also known as *Dengzhan asarum*, was evaluated against NSCLC cells. Sun and colleagues (2018) assessed its efficacy on A549 (IC_{50} 0.43 μg/mL) and A549/DDP cells (IC_{50} 16.07 μg/mL) and noted an elevation in LC3-II levels. Remarkably, co-administration of cisplatin and scutellarin enhanced cisplatin-induced autophagy by suppressing the c-mesenchymal-epithelial transition factor (c-Met)/AKT signalling pathway. This combined treatment reduced the phosphorylated c-Met and AKT levels, significantly augmenting the anticancer effects of cisplatin [83]. Additionally, the cytotoxic effect of scutellarin-induced autophagy significantly contributes to apoptosis, thereby playing a crucial role in overcoming cisplatin resistance in A549/DDP cells [84]. In addition, the inhibition of autophagy by HCQ contributed to cisplatin resistance. These findings were corroborated *in vivo*, where co-administration of cisplatin increased LC3-II levels and decreased phosphorylated AKT and c-Met.

Subsequently, Sun and colleagues (2018) conducted further research on scutellarin against additional NSCLC cell lines, specifically PC-9 and H1975, yielding consistent results with elevated LC3-II levels. Furthermore, *in vitro* analysis indicated that scutellarin activated the ERK1/2 signalling pathway while inhibiting the AKT pathway. These molecular

alterations strongly correlated with autophagy induction by scutellarin, as evidenced in *in vivo* experiments using a mouse xenograft model, which also demonstrated increased LC3-II and phosphorylated ERK1/2 levels alongside decreased phosphorylation of AKT. Additionally, a similar pattern to previous findings emerged, where HCQ-mediated autophagy inhibition led to reduced apoptosis and decreased anti-proliferative capacity [52]. In light of these findings, scutellarin has emerged as a promising candidate for further exploration in cancer therapy. Its potential lies notably in its ability to target autophagy-related pathways for therapeutic interventions.

5.5. Flavones targeted autophagy in cancer cells

Among the 23 chromone-based compounds identified, most belonged to the flavone class. The compounds were oroxylin A (**10**), 5-acetyloxy-6,7,8,4′-tetramethoxyflavone (**11**), chrysoeriol (**12**), norwogonin (**13**), eupafolin (**14**), hispidulin (**15**), wogonin (**16**), chrysin (**17**), nobiletin (**18**), pectolinarigenin (**19**), sinensetin (**20**), luteolin (**21**), apigenin (**22**), and baicalein (**23**). They exhibited inhibitory effects on cell proliferation, either in a concentration-dependent manner or in both concentration- and time-dependent manner. The IC_{50} values and potent concentrations of these flavone compounds in specific cell lines are detailed in Table 2, demonstrating a considerable range from 3.20 to 244.50 μM. For further elucidation, within the flavone class, compounds **16**–**18** and **20**–**23** displayed both cytoprotective and cytotoxic autophagy inducers, with mechanisms of action that varied depending on the cell type involved. Some studies have utilized siRNA and autophagy inhibitors, such as 3-MA, CQ, HCQ, and Baf A1, to discern the role of autophagy induced by the compound in cancer cells. Detailed explanations of these findings will be incorporated in the relevant paragraphs.

Oroxylin A (**10**), derived from *Scutellariae radix,* has been investigated for its anticancer activity against hepatocellular carcinoma cells (HepG2). Experimental findings revealed significant alterations in autophagy markers, notably elevated levels of Beclin-1And LC3-II, which are indicative of enhanced autophagic activity in cancer cells. Moreover, oroxylin A induced autophagy in HepG2 cells by down-regulating mTOR phosphorylation through modulation of the PI3K-PTEN-AKT-mTOR pathway [85]. Furthermore, validation of the autophagic mechanism was achieved through the application of autophagy inhibitors (3-MA), resulting in the observed suppression of apoptosis, as evidenced by the diminished expression levels of caspase-3 and cleaved PARP.

5-Acetyloxy-6,7,8,4′-tetramethoxyflavone (**11**) is classified as an NPD and is a derivative of tangeritin. Tangeritin itself is a natural product commonly present in tangerine peels. Their therapeutic potential was evaluated through both *in vitro* and *in vivo* assessments. *In vitro* experimentation of **11** was conducted on CL1–5 cells, a subtype of NSCLC cells, and demonstrated an IC_{50} value of 3.2 μM. Remarkably, increased levels of LC3-II, indicative of increased autophagic activity, were observed in both *in vitro* and *in vivo* experiments using a xenograft model. Furthermore, a decrease in the levels of phosphorylated mTOR, AKT, and PI3K was observed in cells treated with compound **11**. Notably, the combined administration of compound **11A**nd 3-MA significantly decreased the levels of LC3-II and expression of apoptosis markers, including cleaved PARP and caspase-3. This result suggests that 3-MA might prevent compound **11**-induced apoptosis in CL1–5 cells by suppressing autophagy [48].

Chrysoeriol (**12**), which is abundantly distributed across various plant kingdoms, including *Coronopus didymus*, *Eurya cilliata* Merr, and *Medicago sativa* L. [86], was investigated for its anticancer activity against lung cancer cells, particularly the A549 cell line, demonstrating a noteworthy IC_{50} value of 15 μM. Remarkably, autophagy was elicited, as evidenced by elevated levels of LC3-II and Beclin-1, along with reduced p62 expression. Additionally, treatment with chrysoeriol resulted in decreased phosphorylation levels of mTOR, AKT, and PI3K in treated cells, indicating its potential to modulate the mTOR/PI3K/AKT signalling pathway [49]. Norwogonin (**13**), a flavone isolated from the roots of *Scutellaria baicalensis*, was evaluated against the colon cancer cell line SW48, revealing an IC_{50} value of 15.5 μM. The authors concluded that norwogonin inhibits the growth of SW48 cells by inducing both apoptosis and autophagy. The observed increase in the levels of both LC3-I and LC3-II supported autophagy induction [87].

Eupafolin (**14**), extracted from *Artemisia princeps*, was examined for its efficacy against B-cell non-Hodgkin lymphoma, specifically OCI-LY-3 cells, and demonstrated a favorable IC_{50} value of 5.06 μM. The upregulation of Beclin-1 expression and reduction in p62 levels substantiated the induction of autophagy by compound **14** in OCI-LY-3 cells. Furthermore, eupafolin inhibited the phosphorylation of AKT, mTOR, and P70S6K proteins, suggesting its potential modulation of the AKT/mTOR/P70S6K signalling pathway. Additionally, the inhibition of autophagy by 3-MA was evident through reduced levels of LC3-II, which consequently suppressed apoptosis, as indicated by the decreased expression of cleaved PARP [88].

Hispidulin (**15**), primarily extracted from *Salvia involucrata*, underwent both *in vivo* (xenograft models) and *in vitro* investigations against prostate cancer, specifically the Du145 and VCaP cell lines, with IC_{50} values approximately 10 μM. Hispidulin demonstrated the ability to enhance autophagy as evidenced by an increase in LC3-II levels. Moreover, its autophagy-enhancing effects are attributed to the activation of peroxisome proliferator-activated receptor γ (PPARγ). This was supported by experiments utilizing the PPARγ antagonist GW9662, in which pretreatment with GW9662 led to a reduction in the autophagy-promoting effects of hispidulin, accompanied by elevated phosphorylation levels of mTOR and S6K1. These findings highlight that hispidulin induced autophagy in Du145 and VCaP cells by activating PPARγ, which was also demonstrated *in vivo* [89].

Wogonin (**16**), another flavone derived from *Scutellaria baicalensis*, was assessed for its anticancer activity against colorectal cancer cells (SW48) [90] and nasopharyngeal carcinoma cells (NPC-TW076 and NPC-TW039) [91], demonstrating IC_{50} values of 8 and approximately 50 μM, respectively. In NPC-TW076 and NPC-TW039 cells, wogonin increased LC3-II and Beclin-1 levels, whereas in SW48 cells, it only elevated LC3-II expression. This investigation revealed that wogonin triggered autophagy by inhibiting the PI3K/AKT and signal transducers and activators of transcription 3 (STAT3) signalling pathways in SW48 colorectal cancer cells. In contrast, it inhibited the mTOR/P70S6K pathway in nasopharyngeal carcinoma cells. However, the inhibition of autophagy by 3-MA promoted apoptosis in nasopharyngeal carcinoma cells, suggesting that wogonin exhibits cytoprotective effects on autophagy in this cell type. Nevertheless, no autophagy inhibitors have been employed against SW48 cells; hence, the determination of cytoprotective or cytotoxic autophagy in this cell type remains inconclusive.

Chrysin (**17**), a natural compound abundantly present in dietary sources, such as honey and propolis, has been examined for its efficacy against breast cancer MCF-7 cells [92] and endometrial cancer HEC 1A Ishikawa cells [93]. The IC_{50} values recorded for MCF-7 and HEC 1A Ishikawa cells were 40 μM and 10 μM, respectively. In MCF-7 cells, chrysin induced autophagy, characterized by increased levels of LC3-II. Meanwhile, in HEC 1A Ishikawa cells, chrysin upregulated LC3-II and Beclin-1 while downregulating p62, which is also indicative of autophagic induction. Chrysin treatment resulted in a considerable accumulation of intracellular ROS in HEC 1A Ishikawa cells, suggesting that ROS accumulation partially mediates the induction of autophagy. Notably, pretreatment with NAC dramatically impeded autophagy, underscoring the role of ROS in chrysin-induced autophagy. Furthermore, increasing concentrations of chrysin correlated with decreased phosphorylation of AKT and mTOR in HEC 1A Ishikawa cells, suggesting that these compounds inhibit the AKT/mTOR signalling pathway. As treatment with chrysin caused a significant accumulation of ROS, this study suggested that chrysin inhibited the AKT/mTOR signalling pathway driven by ROS to stimulate autophagy in endometrial cancer cells. Moreover, chrysin appeared to induce cytoprotective autophagy in

endometrial cancer cells. This effect was evidenced by the activation of apoptosis and the inhibition of cell proliferation, which were enhanced by the inhibition of autophagy by CQ.

Nobiletin (**18**), derived from *Citrus depressa* Hayata, has been investigated against pancreatic cancer MIAPaCa-2 cells (IC_{50} 6.12 μM) [94] and gastric cancer SNU-16 cells (IC_{50} doubled from that of pancreatic cancer, 12.5 μM) [95]. In both cell types, nobiletin induced autophagy, as evidenced by the elevated levels of LC3-II and decreased levels of p62. Moreover, in SNU-16 cells, there was a reduction in phosphorylated AKT and mTOR levels, indicating that nobiletin could inhibit the AKT/mTOR signalling pathway. However, nobiletin induces cytoprotective autophagy in gastric cancer cells. This effect was demonstrated by the activation of apoptosis, as evidenced by an increase in cleaved PARP and the inhibition of cell proliferation when CQ inhibited autophagy.

Pectolinarigenin (**19**), a flavone extracted from *Chromolaena odorata*, has garnered scientific interest for its potential therapeutic applications against various cancer types, including hepatocellular carcinoma cells (SK-HEP-1) [96] and gastric cancer cells (AGS and MKN28) [97]. In SK-HEP-1 cells, pectolinarigenin demonstrated the ability to induce autophagy. This induction of autophagy was evidenced by a notable increase in LC3-II, LC3-I, and Beclin-1 levels, concomitant with a reduction in p62 levels. Conversely, in AGS and MKN28 cells, a similar increase in LC3-II and reduction in Beclin-1 levels were observed following treatment with pectolinarigenin. These findings suggest that pectolinarigenin promotes the conversion of LC3-I to LC3-II, triggering Beclin-1-independent autophagy through an increased LC3-II/LC3-I ratio [97]. Furthermore, mechanistic insights revealed that in AGS and MKN28 cells, pectolinarigenin-induced autophagy was mediated by inhibition of the PI3K/AKT/mTOR pathway. These findings underscore the potential of pectolinarigenin as a promising candidate for further exploration in cancer therapy, particularly for targeting autophagy-related pathways.

Sinensetin (**20**), isolated from *Orthosiphon stamineus*, was examined against hepatocellular carcinoma (HepG2 cells) [98] and T-cell lymphoma (Jurkat cells) [99]. Sinensetin exhibited the capacity to induce autophagy in both cell types. This induction was substantiated by elevated levels of LC3-II and Beclin-1 coupled with a reduction in p62 levels. Furthermore, in HepG2 cells, sinensetin stimulated the activation of the p53/AMPK/mTOR signalling pathway, leading to autophagy. Notably, treatment with sinensetin significantly augmented phosphorylated AMPK levels, while diminishing phosphorylated mTOR and p53 protein levels [98]. p53 is crucial for impeding cell development and proliferation in response to oxidative stress and genotoxic signals and serves as a key regulator of autophagy [100]. Its degradation is linked to AMPK activation and mTOR inhibition [101].

Additionally, the accumulation of ROS partly contributes to the induction of autophagy by sinensetin in Jurkat cells. Furthermore, pretreatment with NAC significantly impeded autophagy, suggesting that ROS mediated the induction of autophagy by sinensetin in Jurkat cells. Moreover, as the concentration of sinensetin increased, the levels of phosphorylated AKT and mTOR decreased, indicating the role of sinensetin in inactivating the AKT/mTOR signalling pathway. The authors reported that sinensetin promoted autophagy by turning on the ROS/JNK signalling pathway and shutting off the mTOR/AKT signalling pathway [99]. Following these observations, contradictory outcomes emerged upon co-treatment with sinensetin and 3-MA in both the cell types. Notably, a significant increase in cell viability was observed in HepG2 cells, suggesting that sinensetin-induced suppression of HepG2 cell growth was attributed to autophagic cell death. Conversely, co-treatment reduced cell viability and induced apoptosis in Jurkat cells, indicating the presence of cytoprotective autophagy.

Luteolin (**21**), a flavone commonly found in various plant sources, including vegetables, fruits, and medicinal herbs, has been investigated for its potential therapeutic effects against multiple types of cancer. Studies have demonstrated its efficacy in lung cancer (NCI-H460 cells) [102], hepatocellular carcinoma (SMMC-7721, Hep3B and HepG2 cells) [103,104], colon cancer (SW620 cells) [105], and gliablastoma (A172 and U-373MG cells) [106]. Mechanistically, it has been observed that luteolin induced autophagy across these cancer cell lines, as evidenced by increased levels of LC3-II (in all cells) and Beclin-1 (in SMMC-7721And SW620 cells), along with a reduction in p62 (in Hep3B and HepG2 cells). However, the co-administration of autophagy inhibitors, such as Baf A1 (NCI-H460), CQ (SMMC-7721, Hep3B, and HepG2), and 3-MA (SW620, Hep3B, HepG2, A172, and U-373MG), yielded disparate outcomes among the cell lines. Notably, luteolin exhibited pro-autophagic cell death properties in NCI-H460 and SMMC-7721 cells, as evidenced by a reduction in apoptotic cell death upon autophagy inhibition. Conversely, in the remaining cell lines, luteolin acted as an inducer of cytoprotective autophagy, as the inhibition of autophagy led to decreased cell viability and increased apoptotic cell death. In summary, these findings suggest that the effects of luteolin on autophagy modulation vary across different cell lines, with its roles ranging from stimulating autophagic cell death to inducing cytoprotective autophagy.

Apigenin (**22**), a flavone abundantly present in natural sources such as fruits and vegetables, has been investigated for its anticancer properties against various malignancies, including papillary thyroid carcinoma (BCPAP cells) [107], gastric cancer (AGS and SNU-638 cells) [53], cancer colon cells (HT-29 and HCT1166 cells) [108,109], and hepatocellular carcinoma (HepG2 cells, and *in vivo* studies on nude mice) [110]. Studies have demonstrated that apigenin induced autophagy in these cancer cell lines, as evidenced by the upregulation of LC3-II (observed in all cell lines), Beclin-1 (observed in all cell lines except HCT116), ATG5 (observed in AGS, SNU-638, and HepG2), and the downregulation of p62 (observed in all cell lines except HCT116 and HepG2). Furthermore, additional investigations revealed that apigenin induced a significant increase in intracellular ROS levels in BCPAP cells, which, at least in part, contributed to its autophagy-inducing effects. In gastric cancer cells, apigenin attenuates mTOR phosphorylation, enhances AMPKα and ULK1 activation, and triggers autophagic cell death through protein kinase R-like ER kinase (PERK) signalling, thereby activating the endoplasmic reticulum (ER) stress response. Interestingly, suppression of PERK inhibited apigenin-induced autophagy and prolonged cell survival. Moreover, in gastric cancer cells, apigenin inhibits enhancer of zeste homologue 2 (EZH2) and hypoxia-inducible factor 1-alpha (HIF-1α) under both normoxic and hypoxic conditions, thereby promoting autophagic cell death [53].

Furthermore, apigenin induced autophagy by inhibiting the mTOR/PI3K/AKT signalling pathway in HT-29 cells and the PI3K/AKT/mTOR pathway in HepG2 cells. Subsequent co-administration of autophagy inhibitors, including 3-MA, in BCPAP, HT-29, HCT116, and HepG2 cells, along with siRNAs targeting LC3B and ATG5 in AGS and SNU-638 cells, yielded varied outcomes among the cell lines. Specifically, in BCPAP, AGS, and SNU-638, apigenin exhibited pro-autophagic cell death characteristics, as evidenced by increased cell viability upon autophagy inhibition and reduced levels of LC3-II and ATG-5 observed in AGS and SNU-638 cells. Conversely, in HCT116 and HepG2 cells, apigenin functions as an inducer of cytoprotective autophagy, with autophagy inhibition leading to reduced cell viability and increased apoptotic cell death, as indicated by elevated cleaved PARP and caspases. These observations highlight the contextual nature of apigenin's influence on autophagy, encompassing a spectrum that promotes autophagic cell death to foster cytoprotective autophagy across diverse cancer cell lines.

Baicalein (**23**), another compound derived from the root of *Scutellaria baicalensis*, has been evaluated for its efficacy against various cancer cell lines, including breast cancer (MCF-7 and MDA-MB-231 cells *in vitro* and nude mice *in vivo*) [111], prostate cancer (PC-3 and DU145 cells) [112], and glioma (U251 cells) [26], thyroid cancer (MDA-T68 cells) [113], gastric cancer (SGC-7901And SGC-7901/DDP cells) [114], ovarian cancer cells (HEY cells) [115], and oral squamous cell carcinoma (Cal27 cells). Treatment with baicalein has been shown to induce autophagy in these cell lines, characterized by elevated levels of LC3B-II (across all cell lines) and Beclin-1 (except in PC-3 and DU145 cells), and

reduced levels of p62 (specifically observed in Cal27 cells). In HEY cells, Beclin-1 silencing with Beclin-1 siRNA significantly reduced baicalein-induced LC3-II expression, proving that Beclin-1 is essential for baicalein to induce autophagic flux [115]. Additionally, baicalein-induced cell death has been linked to autophagy modulation through inhibition of the PI3K/AKT signalling pathway in breast cancer, activation of AMPK leading to ULK1Activation and mTOR/Raptor inhibition in prostate cancer, induction of the AMPK signalling pathway in glioma, and inhibition of the AKT/mTOR signalling pathway in gastric cancer.

Additionally, baicalein treatment resulted in significant intracellular ROS accumulation in Cal27 cells, which contributed to the induction of autophagy. Pretreatment with NAC effectively attenuated autophagy, indicating that ROS mediated baicalein-induced autophagy. Moreover, thyroid cancer cells treated with baicalein exhibited a significant increase in nuclear factor kappa B (NF-κB) protein, which serves as a signal for cell autophagy [113]. Furthermore, baicalein administration led to a concentration-dependent increase in ERK phosphorylation, indicating that ERK was activated by baicalein in HEY cells. These findings demonstrated that ERK controlled baicalein-induced autophagy in HEY cells, at least in part, by inhibiting the production of LC3-II when ERK was knocked down using siRNA [115]. Notably, baicalein induced cytoprotective autophagy in ovarian cancer (HEY cells) and oral squamous cell carcinoma (Cal27 cells), as evidenced by reduced cell viability and increased cell death upon autophagy inhibition using CQ and BafA1, respectively, as indicated by the increased levels of cleaved PARP. The effect of baicalein treatment on other cell lines could not definitively ascertain whether it induced autophagic cell death or cytoprotective autophagy, as co-treatment with autophagy inhibitors has not yet been conducted.

5.6. Statistical analysis and future directions

In this systematic review, 23 chromone compounds were analysed for their ability to modulate the autophagy pathway in cancer cells (see Table 2). Notably, all the chromones reviewed induced autophagy activation, resulting in either cancer cell death or cytoprotective effects. Approximately 30 % of these compounds exhibited cytoprotective effects through the activation of autophagy (see Table 2). Importantly, no instances were observed where autophagy inhibition by these natural chromones led to cancer cell death. This is significant because, as highlighted in the introduction, autophagy inhibition is another mechanism that can induce cancer cell death, a strategy that has been investigated in numerous studies and is utilized by several marketed drugs. While these findings are encouraging, it is important to acknowledge several limitations of this review. The included studies employed a variety of experimental models, including both *in vitro* and *in vivo* systems, which introduces variability and limits direct comparability. Additionally, there was heterogeneity in experimental conditions, including differences in cancer cell lines, compound concentrations, treatment durations, and autophagy markers. Moreover, due to the diversity in study designs and data reporting formats, a formal quantitative meta-analysis could not be performed.

Given these limitations, a qualitative synthesis complemented by statistical evaluation was conducted to explore how natural chromones modulate autophagy-related proteins. To further clarify their specific effects, the activation and inhibition frequencies of various autophagy-related proteins were statistically analysed. The chi-square analysis of these frequencies revealed a statistically significant difference ($\chi^2 = 94.03$, df = 12, $P < 0.0001$, see Fig. 5), indicating that the distribution of activation and inhibition is not uniform across the analysed pathways and proteins. This suggests that specific targets are preferentially modulated by chromones, reflecting their distinct roles in autophagy regulation and cancer cell dynamics. For example, PI3K was inhibited by 9 chromones (and not activated by any), while 18 chromones inhibited AKT. Similarly, mTORC1 inhibition was observed with 16 chromones. These findings align with the established roles of these proteins in

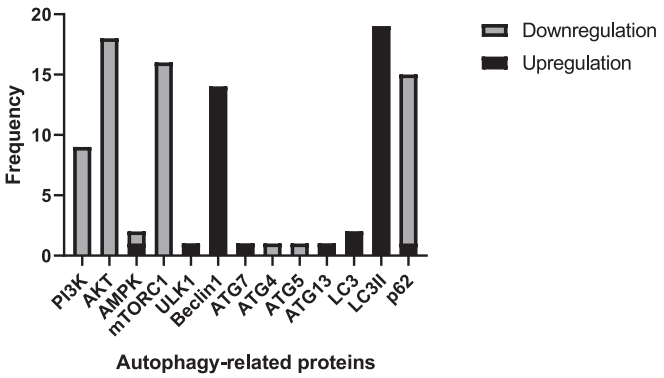


Fig. 5. Distribution of activation and inhibition of autophagy-related proteins by chromone compounds. Chi-Square analysis: $\chi^2 = 94.03$, df = 12, $P < 0.0001$.

promoting cell survival and proliferation [116], where their inhibition facilitates autophagy induction, potentially acting as a tumour-suppressive mechanism [117–119]. Conversely, certain targets showed dominant activation. Beclin1 was activated by 14 chromones and inhibited by none, while LC3II activation was observed with 19 chromones. Beclin 1 is pivotal for autophagosome formation [120], whereas the conversion of LC3-I to LC3-II is essential for autophagy progression [121], underscoring their roles as critical regulators in the autophagy pathway.

From a broader perspective, the results highlight distinct roles among functional groups of autophagy-related proteins. Signalling regulators such as PI3K, AKT, and mTORC1 were primarily inhibited by 78 % of the chromone compounds, reflecting their importance as therapeutic targets for disrupting cancer cell survival pathways, particularly in the initiation phase of autophagy. On the other hand, autophagy effectors, such as the upregulation of LC3II in 83 % of chromones and Beclin1 in 60 % of studied chromones, along with the reduction of p62 in 60 % of chromones, highlight their critical roles in autophagy progression and maturation. The modulation of these proteins highlights their crucial role in maintaining autophagic flux during therapy. These findings suggest that chromones exert their anticancer effects, at least in part, by selectively inhibiting the PI3K/AKT/mTOR pathway while simultaneously modulating key autophagy components, such as LC3II, Beclin1, and p62. This dual modulation strategy appears to promote autophagy-mediated cancer cell death, suggesting that chromones could potentially enhance the effectiveness of existing therapies, such as chemotherapy and immunotherapy, by modulating autophagy to help overcome treatment resistance.

Importantly, this review reveals that none of the natural chromones examined inhibited autophagy as a means to induce cancer cell death, a therapeutic strategy already employed by multiple clinically approved drugs. In contrast, synthetic chromone-based compounds, including natural product mimic (NPM) derivatives, have demonstrated this capability, suggesting a functional distinction between natural and synthetic variants. For instance, Shamsudin and colleagues reported autophagy inhibition by synthetic chromones in colon cancer cells [20], while Sakagami and co-workers observed similar effects in oral squamous cell carcinoma cells [122]. These distinctions highlight the functional divergence between natural and synthetic chromones and underscore the need for future studies focused on optimising synthetic analogues with enhanced autophagy-inhibiting activity, improved potency, and reduced off-target effects. Additional research into the pharmacokinetics, toxicity profiles, and delivery systems of chromone derivatives is also essential to bridge preclinical findings with clinical applications. Overall, the mechanistic insights and statistical trends presented in this review offer a foundation for the continued development of chromone-based compounds as therapeutic agents targeting autophagy in cancer.

6. Conclusion

Chromones are a class of natural product-based compounds known for their diverse biological activities, particularly anticancer potential. Increasing evidence suggests that chromones modulate autophagy, a process critically involved in tumour development and progression. This systematic review aimed to evaluate chromone-based compounds that modulate autophagy in cancer models, especially given the lack of systematic literature reviews exploring whether chromones modulate autophagy to induce cancer cell death. From an initial pool of 568 records published between 2004 and 2024, 44 eligible studies were reviewed, covering 23 chromone derivatives including flavones, isoflavones, and biflavonoids. Most compounds activated autophagy and led to the death of cancer cells, while a few displayed cytoprotective effects. Among them, the flavone subclass demonstrated the highest potential for modulating autophagy and suppressing cancer cell growth. However, none of the natural chromones were reported to inhibit autophagy as a strategy for inducing cancer cell death, a mechanism successfully exploited by synthetic analogues. Mechanistically, chromones were found to inhibit PI3K/AKT/mTORC1 signalling while activating autophagy markers such as LC3-II and Beclin-1, and downregulating p62. This review acknowledges several limitations, including heterogeneity in experimental models, variability in assay conditions, and the absence of *in vivo* or clinical data in many studies.

Looking forward, chromones appear to exert anticancer effects by selectively targeting both upstream signalling regulators and core autophagy machinery. This dual modulation suggests their potential in enhancing the efficacy of chemotherapy and immunotherapy by overcoming resistance mechanisms. Future research should focus on optimising synthetic chromone analogues for autophagy inhibition, particularly in cancer types where this pathway promotes tumour survival. Additionally, further studies should explore pharmacokinetics, toxicity, and formulation strategies, as well as the combinatory potential of chromones with apoptosis-inducing or immune-modulating agents. Overall, this review highlights the untapped potential of chromone-based compounds as autophagy-targeting agents and lays a foundation for their future development in cancer therapeutics.

Authors contribution

K.R. played a pivotal role in the conceptualisation of the study and served as the project leader. N.F.S. and A.R.M.N. carried out the systematic literature review, investigations, and data analysis, and were responsible for drafting the original manuscript and preparing visualisations. I.J. and E.S. contributed to the experimental design and manuscript preparation. Furthermore, M.A.A., S.L.C., N.S., S.I., S.W.L., F.N., H.S., and S.S. were involved in data interpretation, as well as in the editing and reviewing of the manuscript.

CRediT authorship contribution statement

Nur Farisya Shamsudin: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Amira Rusyda Mat Nawi:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Ibrahim Jantan:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Emil Salim:** Writing – review & editing, Validation, Methodology, Data curation. **Maryam Aisyah Abdullah:** Writing – review & editing, Validation, Methodology, Formal analysis. **Suet Lin Chia:** Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Norazalina Saad:** Validation, Supervision, Investigation, Formal analysis. **Syahrul Imran:** Writing – review & editing, Validation, Supervision, Methodology. **Sze-Wei Leong:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis. **Firzan Nainu:** Writing – review & editing, Funding acquisition. **Hafid Syahputra:** Writing – review & editing, Funding acquisition. **Suryati Syafri:** Writing – review & editing, Funding acquisition. **Kamal Rullah:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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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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Data availability

No data was used for the research described in the article.

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