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Review

Recent advances in glioblastoma multiforme therapy: A focus on autophagy regulation

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ABSTRACT

Despite conventional treatment options including chemoradiation, patients with the most aggressive primary brain tumor, glioblastoma multiforme (GBM), experience an average survival time of less than 15 months. Regarding the malignant nature of GBM, extensive research and discovery of novel treatments are urgently required to improve the patients' prognosis. Autophagy, a crucial physiological pathway for the degradation and recycling of cell components, is one of the exciting targets of GBM studies. Interventions aimed at autophagy activation or inhibition have been explored as potential GBM therapeutics. This review, which delves into therapeutic techniques to block or activate autophagy in preclinical and clinical research, aims to expand our understanding of available therapies battling GBM.

1. Introduction

According to the World Health Organization (WHO), glioblastoma multiforme (GBM) is the most widespread and malignant brain neoplasm [1], with a median lifespan of around 14.6 months, representing about 50 % of all brain gliomas [2]. The protocols for controlling GBM include complete resection and subsequent radiotherapy and chemotherapy with the temozolomide (TMZ) [3]; nonetheless, most GBM cancers develop within two years [4,5]. The aggressive spread and growth of GBM are mainly due to the tumor's resistance to radiation and chemotherapy [6,7]. Furthermore, it is impossible to entirely remove GBM cells with surgical procedures because they invade and infiltrate the surrounding tissue, leading to tumor recurrence [8,9]. Accordingly, strengthening treatment protocols to overwhelm resistance is urgently needed [10]. In the past few years, researchers have discovered that the cellular recycling system (i.e., autophagy) plays a crucial function in developing radio- and chemo-resistance in human malignancies, including GBM [11,12]. However, some investigations have considered autophagic death as a therapeutic approach [13,14].

Autophagy is a process through which defective proteins and organelles are broken down and removed. Several essential active proteins, including the UV radiation resistance-associated gene (UVRAG), autophagy-related proteins (Atg), phosphatidylinositol 3-kinase catalytic subunit 3 (PIK3C3), light chain 3 (LC3), Beclin-1, and ubiquitin-binding protein (p62), initiate the autophagy process. These proteins work together to generate double-membrane autophagosomes, breaking

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down internal substances by fusion with lysosomes [15]. Autophagy is activated by various stressors, such as nutrition shortage, organelle injury, and excessive protein buildup [16,17]. In this regard, healthy cells use basal autophagy levels to ensure a supply of essential nutrients as an energy source and maintain biological function, homeostasis, and the disposal of old proteins and harmed organelles [18]. Critical pathways, mainly the mammalian target of rapamycin (mTOR) signaling, play crucial roles in autophagy regulation. Autophagy is increased once mTORC1 is suppressed under specific stressful conditions, including organelle injury and starvation. Numerous findings have proposed that autophagy is induced by mTORC1 suppression and AMP-activated protein kinase (AMPK) induction [19,20]. Importantly, autophagy controls the production of tumor suppressors like p53, which is negatively regulated by mTOR and AMPK expression. In comparison, mTOR may activate oncogenes, resulting in autophagy suppression and cancer development by restricting protein breakdown in oxidatively challenged cells [21]. On the other hand, autophagy arises significantly in various types of tumors, including KRAS- and BRAF-driven cancer, maintaining an elevated basal status of autophagy [22]. RAS is a small GTPase that interacts with RAF and affects cell proliferation, survival, and metabolism. Its mutations are attributed to the evolution of lethal tumors such as lung, colon, and pancreas cancers as well as brain metastasis [23–25]. Several findings have shown that RAS-mutated cells experience increased levels of autophagy, and their survival depends on autophagy throughout nutrient starvation. Autophagy-related protein inhibition thus reduces the cells' proliferation and increases the aggregation of damaged mitochondria [26]. These determinations propose that autophagy has contradicting roles in different tumors depending on their specifics.

Furthermore, the involvement of autophagy in cancer treatment is complicated and looks like a double-edged sword [27]. Exposing cancer cells to chemotherapeutics or ionizing radiation provokes autophagy, which critically affects the effectiveness of treatment [28]. Robust activation of autophagy may propagate a non-apoptotic cell death pattern by inducing extensive self-digestion in cancer cells, augmenting the cytotoxic effects of numerous anti-cancer compounds [29–32]. In contradiction, autophagy might serve as a cytoprotective phenomenon for the cancer cell to escape from the cytotoxic treatments accompanied by poor clinical outcomes [33,34]. Accordingly, autophagy suppression in the case of treatments that augment cytoprotective autophagy could be a beneficial approach to increase the success rate of anti-cancer regimens [35]. More interestingly, autophagy modulation in cancer cells may suppress other cancer-related mechanisms involved in tumor growth and invasion [36,37]. Today, the critical issue is determining the exact situations in which autophagy inhibitors or activators boost treatment efficiency. There is compelling evidence that autophagy regulation is vital for GBM cells; nevertheless, the precise role of autophagy in GBM treatment is still an open question. To date, numerous naturals and chemicals have been introduced as cancer autophagy modulators to aid the anticancer impact of chemotherapeutics [38–42]. Notably, recent advances in nanotechnology provide a plethora of options for fighting cancer with novel and efficient therapeutic agents that overcome the challenges encountering standard medications, including off-target effects and poor targeted delivery [43–45]. Furthermore, certain nanomaterials have the ability to regulate autophagy and have been used as cancer therapeutics [46]. The involvement of autophagy in current therapeutic modalities and recruiting autophagy modulators in cancer therapy are addressed below with a focus on GBM.

2. Role of autophagy in preclinical cancer research

2.1. Effect of autophagy on tumor initiation and growth

Autophagy has long been considered a tumor suppressor phenomenon due to discovering the function of the Beclin-1 complex in tumor suppression [47]. Deletion or mutation of genes encoding Beclin-1 or its interacting proteins (e.g., UVRAG and endophilin B1) has been linked to a greater incidence of tumor types in vitro and in vivo [48,49]. Furthermore, downregulation or frameshift mutation of many Atg genes has been implicated in human malignancies [50]. Autophagy, in general, is thought to inhibit carcinogenesis at an early stage by eliminating oxidative stress-induced genomic instability and inflammation as critical inducers of tumor growth [51,52]. Omission of the Atg5 and Atg7 genes was consistently reported to induce benign tumors in the liver and pancreas of tumor-prone mouse models but never progressed to a malignant tumor [53,54]. The same results were found in melanoma, prostate, and lung cancer, where genetic inhibition of Atg5 and Atg7 slowed tumor development, possibly owning to the impaired metabolism (i.e., attenuated fatty acid oxidation and glycolytic flux), expansion of destroyed mitochondria, and significant DNA lesions in tumor cells [55–60]. These findings indicate that, whereas autophagy is critical to inhibit tumor onset, it is required to grow malignant tumors since it helps malignant cells to cope with nutrient shortage, hypoxia, and other tensions in the tumor environment. This concept may not necessarily apply to the participation of autophagy in all malignancies, and contradicting data occur owing to a variety of circumstances, such as tumor type, genetic state, tumor stage, and tumor environment [61].

Autophagy in nontumor cells in the tumor microenvironment (TME) provides nutrients necessary for cancer progression since malignant cells are often arginine auxotrophs due to the lack of enzymes needed for arginine synthesis [62]. Of note, autophagy in pancreatic stellate cells induced by pancreatic ductal adenocarcinoma (PDAC) was reported to increase arginine secretion, fueling tumor cell metabolism and growth [63]. In KRAS-driven cancers, autophagy suppression also reduces circulating arginine and tumor proliferation [64]. Another work in a Drosophila melanogaster model has shown that transplanting autophagy-deficient, inactivated tumors into autophagy-proficient hosts reactivates tumor development through tumor necrosis factor (TNF) and interleukin (IL)− 6-like signaling. Hence, through nutrient-generating autophagy, transformed cells recruit surrounding normal cells as crucial microenvironmental participants in tumor growth [65]. More critically, conventional chemotherapeutics generally cause cytoprotective autophagy in tumor cells, reducing their ability to fight cancer; hence, co-administering autophagy inhibitors with standard therapy may enhance its efficacy and lower the risk of developing chemo- or radio-resistance [66]. For example, suppression of KRAS or inhibition of its pharmacological effectors, e.g., extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) in a PDAC model boosted autophagic flux, and the addition of an autophagy inhibitor improved therapeutic effectiveness [67]. Suppressing autophagy using a hydroxychloroquine (HCQ) analog has recently been discovered to promote the radiosensitivity of PDAC cells in vitro and in vivo [68]. Likewise, restricting autophagy in BRAF (V600E)-driven tumors was shown to reduce their resistance to vemurafenib, a BRAF inhibitor [69]. In addition, the metabolic changes generated by the inhibition of autophagy might impair cancer stem cell stemness [70]. Mutations in essential autophagy proteins in breast cancer-bearing mice have been demonstrated to diminish the tumor-initiating capacity of certain cancer stem cell types by compromising the transducer and activator of transcription 3 (STAT3) or transforming growth factor-β (TGF-β)/Smad signaling pathways [71]. Autophagy inhibition in combination with tyrosine kinase inhibitors (e.g., nilotinib and dasatinib) was also found to completely eradicate functional stem cells in chronic myeloid leukemia (CML) [72]. Thus, autophagy inhibitors might be used as adjuvant therapy for cancer patients.

Importantly, addressing whether autophagy facilitates or represses tumor development requires a thorough understanding of its involvement in the TME immune function [73]. Autophagy may impact the ability of immune cells to identify malignant cells [74]. It has been reported that immunogenic cell death during chemotherapy necessitates autophagy in tumor cells, facilitating the infiltration of anticancer dendritic cells and T-lymphocytes [75]. Moreso, triggering autophagy

via nutrient deprivation in autophagy-competent lung tumor cells has been shown to deplete T-regulatory cells, improving anti-cancer immunosurveillance in a KRAS-mutated lung tumor in vivo [76]. Accordingly, preserving and even activating autophagy in tumor cells may promote TME immune function; however, contradicting results show that autophagy induction reduces the antitumor efficacy of natural killer (NK) cells under hypoxic settings [77,78]. Autophagy suppression has been found to inhibit protein phosphatase 2A (PP2A) activity and increases c-Jun N-terminal kinase (JNK)-mediated CC chemokine ligand 5 (CCL5) expression that improves NK cell attraction and infiltration [79]. Notably, autophagy suppression in tumor-associated macrophages (TAMs) transforms the M2 phenotype into the M1 phenotype, suppressing tumor growth [80]. Moreover, inhibition of autophagy induces a metabolic shift in CD^{8+} T lymphocytes, causing them to obtain an effector memory phenotype and generate more interferon-γ (IFN-γ) and TNF-α [81,82]. It has also been indicated that suppressing autophagy during cancer immunotherapy with IL-2 increased immune cell multiplication and infiltration and prolonged tumor relapse periods [83]. The disparity in the findings may be due to a lack of attention paid to the differences between LC3-associated phagocytosis (LAP) and canonical autophagy [84]. Some proteins (e.g., Atg5 and Atg7) are common in these processes, and genetic inhibition of the mentioned proteins failed to target each pathway in isolation [85]. In this regard, TAMs and T cell phenotypic alterations and increased cytokine production were seen in response to LAP, but not conventional autophagy [86]. In a nutshell, the TME's immune system seems to benefit from the stimulation of autophagy and LAP reduction.

In addition, malignant cells react differently to autophagy regulation regarding their genetic context [87]. For example, tumors with increased MAPK activation may be more vulnerable to autophagy inhibition. In this regard, significant sensitivity to autophagy suppression was identified in various cancers, including PDAC, where RAS mutations activate the ERK signaling pathway [59,88]. Tp53 (i.e., p53 protein-encoding gene) is another possibility for regulating cancer cells' reaction to autophagy. It has been reported that silencing Atg5 and Atg7 in the presence of p53 inhibited tumor development in a PDAC model but accelerated tumor growth in the lack of p53 [89]. Similarly, autophagy inhibition in lung cancer with a KRAS mutation resulted in p53-dependent tumor cell death, and silencing p53 abolishes the anti-tumor effects [55]. Furthermore, luteolin has been shown to suppress autophagy in p53 wild-type colon cancer cells but not in p53 mutant cells [90]. In contradiction, although Atg7 deficiency triggers p53-mediated tumor cell death in BRAF mutation-induced lung cancer, p53 omission did not affect Atg7 null tumor proliferation [91]. Furthermore, autophagy suppression was shown to increase the chemosensitivity of BRAF-mutated brain tumors [92]. Accordingly, expanding our understanding of how the genetic background of cancer influences the therapeutic value of autophagy regulation appears to be crucial.

2.2. Effect of autophagy on tumor cell survival

Autophagic death is the most paradoxical cell death process identified as a possible protection against oncogenic transformation [93]. Actually, autophagy is a prosurvival mechanism that, when impaired, results in cell death patterns. It is, therefore, likely to think of autophagic cell death as a kind of cell death that only uses autophagic cargoes [94]. In this regard, autophagic cell death has been considered a preventive procedure against RAS-mediated oncogenesis. Byun et al. revealed that malignant cells overexpressing RAS oncogenes have upregulated JNK signaling accompanied by Atg5 expression as well as autophagic cell death [95]. Surprisingly, reactive oxygen species (ROS) generating agents were shown to promote autophagic cell death in HeLa cells but not normal cells, and suppressing apoptosis inhibits autophagy and cell death [96]. Likewise, etoposide-induced DNA damage was demonstrated to induce Bcl-2 interacting protein 3 (BNIP3)-mediated autophagic death in apoptosis-competent breast cancer cells under hypoxic conditions [97]. In keeping with these findings, the autophagy machinery has been included in the tumor-suppressive crisis mechanism (the ultimate barrier preventing oncogenesis), emphasizing that autophagy cargo impairment may be necessary for cancer development [98].

Notwithstanding the findings mentioned above emphasizing the explicit function of autophagy in cancer cell extinction, several investigations have shown the indirect impacts of autophagy through influencing apoptosis. However, depending on the conditions, autophagy may either suppress or cause apoptosis [99]. Intriguing research done by Gump et al. demonstrated that autophagy destroys familial adenomatous polyposis-1 (Fap-1) and accelerates Fas-mediated mitochondrial-independent apoptosis in cancer cells. This effect, however, was stimulus and cell-type-specific, and autophagy may prevent mitochondrial-dependent or TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis [100]. Although the interaction of autophagy and apoptosis is multifaceted, most investigations focus on the antiapoptotic impact of autophagy. In this regard, autophagy activation has long been thought to be a way for cancer cells to avoid apoptosis [101]. Silencing Atg5 and Atg7 or pharmacological suppression of autophagy was reported to trigger caspase-3-mediated attachment-induced apoptosis (anoikis) in RAS-mutated mouse embryonic fibroblasts [102,103]. Furthermore, in silico screening revealed that even human cancer cells lacking RAS mutations may suffer apoptotic death following genetic or pharmacologic autophagy suppression [104,105]. Autophagy inhibition was reported to sensitize cancer cells to apoptosis through upregulating Forkhead transcription factor (FOXO)3a and enhancing the apoptotic protein p53 upregulated modulator of apoptosis (PUMA) gene transcription [106]. Likewise, inhibition of Atg5 was shown to upregulate PUMA and induce complete mitochondrial outer membrane permeabilization [107]. Targeting autophagy via downregulating Beclin-1 has also been demonstrated to yield apoptosis in ovarian cancer Skov3 cells [108]. Besides, by continuously sequestering the large caspase-8 component in autophagosomes and then eliminating it in lysosomes, the TRAIL-mediated autophagic response has been shown to counterbalance the TRAIL-mediated apoptosis [109]. Consistently, impaired autophagosome maturation via Atg2A/B deletion as well as accumulation of autophagosome membrane was demonstrated to induce noncanonical activation of caspase-8 following nutrient starvation [110]. Indeed, the autophagy machinery activates the caspase-8-mediated extrinsic apoptosis pathway. It has been demonstrated that caspase-8 complexes with Atg5 and then colonizes with LC3 and p62 on the autophagosome membrane. Fas-associated death domain (FADD) adapter protein is then coupled to the complex and triggers caspase-8 self-processing and signaling [111]. In light of the evidence described above, one may infer that autophagy inhibition decreases the apoptotic threshold of cancer cells and drives them to die.

Emerging research shows that autophagy is necessary for malignant cells to resist chemotherapy-induced apoptosis, and recruiting autophagy inhibition in conjunction with cytotoxic chemotherapeutics has been demonstrated to accelerate cancer cell death [67,112,113]. Of note, autophagy may be activated downstream of chemotherapy-induced DNA damage or distinct tumor-driving enzyme activation. For example, cisplatin evokes autophagy in cancer cells via inhibiting O-6-methylguanine-DNA methyltransferase (MGMT), and suppressing autophagy by chloroquine (CLQ) was shown to increase the sensitivity of gastric tumor cell to cisplatin in vivo and in vitro [114]. Feiyanning (i.e., Chinese herbal medicine) was consistently demonstrated to eliminate cisplatin-induced protective autophagy and improve the chemosensitivity of A549 lung cancer cells [115]. Another work by Xu et al. found that paclitaxel causes apoptosis and autophagy in MDA-MB-231 triple-negative breast cancer (TNBC) cells and blocks autophagy by knocking down FOXO1, promoting apoptotic cell death [116]. Moreover, a novel autophagy inhibitor, cepharanthine, was shown to sensitize MDA-MB-231 and BT549 TNBC cells as well as xenografted mice to the chemotherapeutic drug epirubicin via enforcing

oxidative mitochondrial fission and apoptosis [117]. Therefore, autophagy inhibitors are promising adjuvants to increase the apoptotic response of cancer chemotherapeutics.

Autophagy also inhibits TNF- and Toll-like receptor (TLR)-mediated necroptosis (i.e., the programmed type of necrotic cell death) through degrading critical proteins, including receptor-activating protein kinase (RIPK)− 1, RIPK-3, TATA-binding protein-1 (TBP-1), and TIR-domain-containing adapter-inducing interferon-β (TRIF) [118]. Thus, pharmacological inhibition of autophagy can synergize the necroptotic effect of cytotoxic drugs such as etoposide and doxorubicin as a therapeutic approach. However, autophagy inhibition has opposing effects in the early stages of cancer since the production of autophagosomes is a key step in mediating cell death during tumor initiation [119]. Consistently, TNF-α activated necroptosis was shown to induce early autophagy [120]. Indeed, autophagosomes can serve as a framework to facilitate the transition between apoptosis and necroptosis. To enable TRAIL-mediated necroptosis, RIPK1 and necrosomes have been demonstrated to be attracted to the autophagosome membrane in tumor suppressor Map3k7-mutated mouse prostate cells in a p62-dependent fashion. Strikingly, inhibition of RIPK or knockdown of p62 shifted necroptosis to apoptosis in response to TRAIL activation [119]. Likewise, inhibition of Bcl-2 using obatoclax was found to stimulate the interaction of Atg5 and necrosome components (e.g., RIP1, RIP3, and FADD), as well as the assembly of necrosomes into autophagosomes. Significantly, suppressing RIP1 and RIP3 prevented obatoclax-induced cell death but not the production of autophagosomes, indicating that RIPs have vital functions in cell death downstream of early autophagy activation [121].

2.3. Effect of autophagy on tumor metastasis

One of the challenging characteristics of cancer treatment is controlling the spread of tumor cells from the preliminary location to other parts of the body (i.e., metastasis). When cancer cells become metastatic, they acquire the capacity to survive and migrate in a detached state [122]. Autophagy probably plays a role in cancer metastasis since multiple clinical studies revealed the superior production of autophagic proteins in human metastatic lesions [123]. Intriguingly, Sharifi et al. found that autophagy suppression inhibited tumor invasion in 4T1 breast cancer and limited lung metastasis in an orthotopic mouse mammary tumor model through LC3-dependent degradation of paxillin, a focal adhesion (FA)-associated adapter protein, and the subsequent disassembly of FAs [124]. Mechanistically, autophagosomes disrupt focal adhesion complexes, which in turn impair the cell-matrix connection points to promote cell motility [125]. Moreover, inducing autophagy via mTORC1 inhibition has been demonstrated to accelerate epithelial-mesenchymal transition (EMT) in A549 lung epithelial cancer cells, a crucial response underlying cancer metastasis [126]. Likewise, autophagy was shown to play a critical function in EMT and the aggression capability of hepatocellular carcinoma cells [127]. Provoking the TGF-β/Smad3-dependent pathway is likely the underlying mechanism for autophagy-induced EMT [128]. There is some evidence that the autophagy-mediated clearance of P-bodies (i.e., RNA processing bodies), critical for TGF-β-induced EMT, requires spleen tyrosine kinase, which may help as a bio-indicator for cancer metastasis [129]. In contradiction, autophagy induction was demonstrated to reduce the expression of MMPs and other pro-EMT proteins through suppressing nuclear factor kappa B (NF-κB) signaling, exhibiting the complicated role of autophagy in the EMT process and metastasis [130–132]. Furthermore, under stress conditions, the tumor suppressor p53 was shown to induce autophagy and inhibit EMT and metastasis [133,134]. It has been argued that elucidating the interaction between autophagy and EMT may deliver new insights into the role of autophagy in the molecular mechanism of cancer metastasis, which has been thoroughly discussed by Babaei et al. [135].

It is critical to note that some autophagy-related proteins may

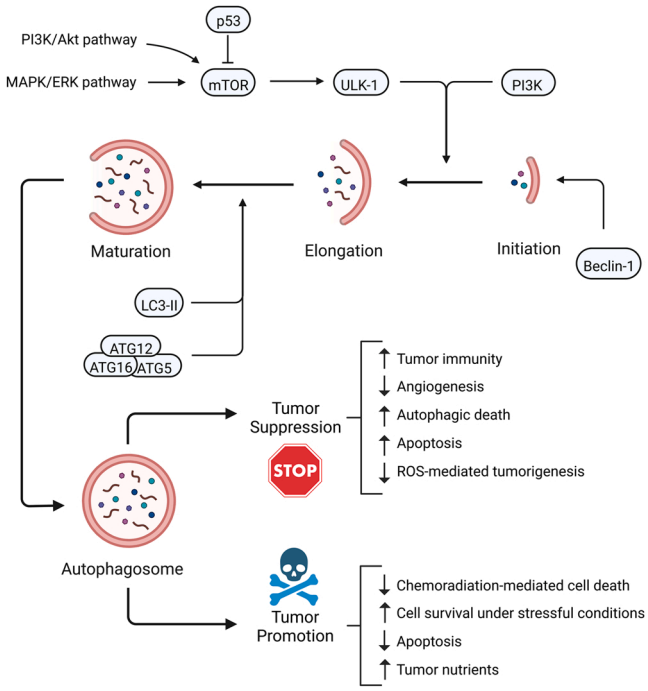

Fig. 1. Schematic diagram of cancer autophagy.

regulate metastatic cancer pathways. The autophagy adapter p62 acts as a molecular connection linking autophagy to malignancy through blocking degradation of the pro-metastatic transcription factor Twist1. It has been demonstrated that autophagy suppression induces p62 accumulation, stabilizing Twist1 and stimulating tumor growth and metastasis [37,136]. In a positive feedback loop, Twsit1 further suppresses autophagy through activating phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling [137]. Besides, it has been postulated that growth factor-induced ubiquitination of essential EMT proteins (e.g., Smad4) improves their interaction with p62, hence preserving their expression and restricting their destruction [138]. P62 was also shown to prolong the mRNA half-life of numerous pro-metastatic proteins in malignant melanoma [139]. According to the mentioned records, the co-suppression of autophagy and p62 was suggested as a practical approach in cancer therapy [140]. However, a contradicting report demonstrated that p62 mediated the selective autophagy of pro-metastatic proteins in breast cancer and suppressed cancer cell motility [141]. Hence, further research into the mechanism of action of p62 inhibitors in malignancies is urgently needed.

In addition, autophagy has a possible function in modulating metastasis at the secondary site. Tumor cells may longley remain dormant (i.e., a nondividing state) before reactivating and reinitiating proliferation at the metastatic site. Since anticancer drugs only target active malignant cells, dormancy facilitates tumor recurrence after initial treatment. Emerging data imply the involvement of macroautophagy in both acquiring and maintaining the dormant phenotype and transforming dormant cells into malignant ones by supplying proper energy balance during metabolic stress and controlling ROS production [142]. As a proof of concept, mTOR signaling as the primary autophagy inhibitor was frequently reported to be impeded in dormant tumor cells [143–146]. Furthermore, dormant tumor cells were shown to be more vulnerable to autophagy targeting than their proliferating counterparts. Notably, inhibition of autophagy through ablation of the Atg7 gene in an animal model of breast cancer resulted in mitochondrial dysfunction, ROS production, and apoptotic dormant cell death [147]. In contradiction, findings from a study on the mouse mammary carcinoma model indicated that although the autophagic flux is upgraded in dormant cells, pharmacologic or genetic suppression of autophagy not only failed

Table 1
Completed clinical trials on the involvement of CLQ and HCQ in the efficacy of anticancer regimens.

Drug regimen	Type of cancer	Phase	Main finding	Reference
HCQ + carboplatin + paclitaxel	Metastatic NSCLC	Ib	– Patients with KRAS-mutated NSCLC may benefit from autophagy inhibition to overwhelm treatment resistance.	[162]
HCQ + everolimus	RCC	I/II	– Most patients were successfully treated, with 67% reporting disease remission and more than 40% reporting a PFS of more than six months.	[163]
HCQ	Resected solid tumors	II	– Plasma levels of the tumor suppressor Par-4 increased by at least twice in almost half of the patients.	[164]
HCQ + temozolomide	Melanoma	I	– The combination is safe and tolerable and drives autophagy regulation as well as stable disease prolongation.	[165]
HCQ + bortezomib	Relapsed or refractory myeloma	I	– Combining autophagy suppression with bortezomib-induced proteasomal inhibition is a possible helpful strategy for improving myeloma therapeutic results.	[166]
HCQ + rapamycin, cyclophosphamide + dexamethasone		I	– The combination showed anti-myeloma activity in about 60% of patients. Adding mTOR and autophagy inhibition gives a tolerable regimen with a durable response.	[167]
HCQ + sirolimus	LAM	I	– The combination was well-tolerated and promoted lung function at the 24-week time point.	[168]
HCQ + dabrafenib + trametinib	Advanced BRAFV600-mutant melanoma	I/II	– The combination was well-tolerated and produced a high response rate as well as favorable PFS, particularly in pretreated patients with raised LDH.	[169]
CLQ + taxanes	Advanced or metastatic anthracycline-refractory breast cancer	II	– As indicated, the combination was safe and effective, with promising ORR and PFS.	[170]
CLQ + gemcitabine	Metastatic or unresectable pancreatic cancer	I	– CLQ was well tolerated and demonstrated encouraging benefits in the clinical response to chemotherapy.	[171]

Abbreviations: CLQ; chloroquine, HCQ; hydroxychloroquine, NSCLC; non-small cell lung cancer, RCC; renal cell carcinoma, PFS; progression-free survival, Par-4; prostate apoptosis-response-4, mTOR; mammalian target of rapamycin, LAM; lymphangioleiomyomatosis, LDH; lactate dehydrogenase, ORR; objective response rate.

to eradicate these cells but also triggered dormant cells to proliferate and invade. The authors argued that dormant cell recurrence leans on autophagy for eliminating metabolic regulators like Pfkfb3 [148]. Further studying the actual regulatory functions and particular targets of autophagy in dormant cancer cells is essential and will undoubtedly improve the management of metastatic and recurrent cancers. The function of autophagy in cancer dormancy has comprehensively been reviewed elsewhere [149]. Overall, cancer cells' response to autophagy as a tumor-promoting or tumor-suppressing factor remains an open question, and a thorough comprehension of the mechanisms that increase autophagic cell death while inhibiting the cytoprotective impact of autophagy is critical for developing a candidate drug for clinical modulation of autophagy in cancer patients. Fig. 1 shows the schematic diagram of cancer autophagy.

3. Clinical significance of autophagy modulation in cancer patients

According to the emerging preclinical proofs concerning the benefits of autophagy alteration in improving the effectiveness of cancer therapies, a variety of autophagy modifiers are developing; however, CLQ and HCQ are the only FDA-approved autophagy blockers for clinical application [150]. Recruiting these drugs has provided an outstanding condition to determine the clinical significance of autophagy manipulation in cancer therapeutic approaches [35]. Early clinical findings showed that CLQ and HCQ inhibit autophagy at well-tolerated levels in cancer patients. Further investigation demonstrated some anticancer effects and clinical advantages of these drugs when combined with traditional chemotherapeutics [151]. For example, a clinical translation of studies concerning the synergistic impact of CLQ plus vemurafenib on lowering BRAF-mutated brain cancer cell viability indicated positive results with this combination treatment in vemurafenib-resistant patients [69,92].

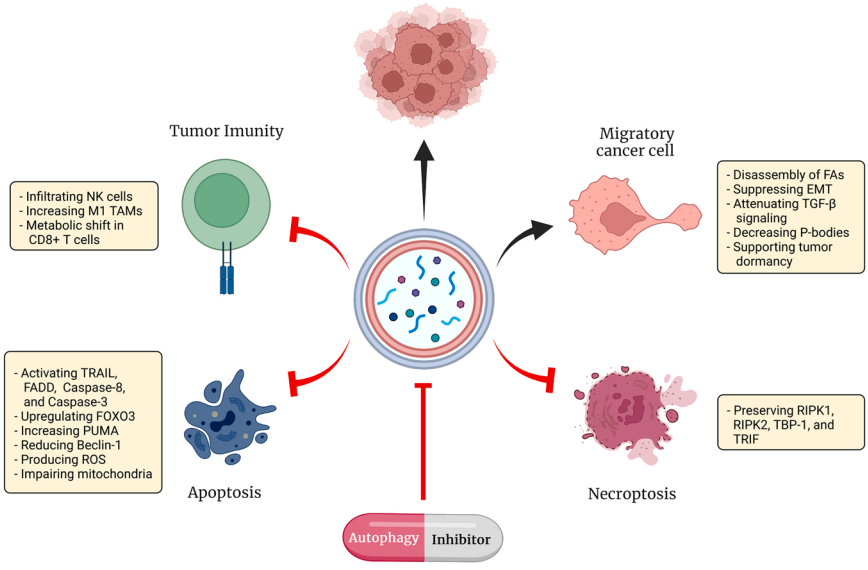

Fig. 2. Potential mechanisms of autophagy inhibitors as promising anticancer candidates. **Abbreviations:** NK; Natural killer, TAMs; Tumor-associated macrophages, TRAIL; Tumor necrosis factor-related apoptosis-inducing ligand, FOXO; Forkhead box O, PUMA; p53 upregulated modulator of apoptosis, ROS; Reactive oxygen species, FA; Focal adhesion, EMT; Epithelial-to-mesenchymal transition, TGF; Transforming growth factor, RIPK; Receptor-interacting protein kinase, TBP; Thioredoxin binding protein.

Furthermore, the mTOR inhibitor temsirolimus and HCQ combination therapy were proven to be safe, well-tolerated, and have strong anti-tumor effects in patients with advanced solid malignancies [152]. Similarly, CLQ was shown to improve patients' overall survival (OS) with primary brain tumors when administered in combination with standard treatments [153,154]. CLQ was also shown to sensitize solid tumor-induced brain metastasis to whole brain irradiation in a phase II clinical study [155]. These findings highlight the need to create innovative, more selective, and efficient autophagy inhibitors to sufficiently comprehend the function of autophagy in clinical cancer biology. (Table 1).

Despite the initially promising findings on using CLQ or HCQ in cancer therapy regimens, some clinical investigations presented opposing results. For example, HCQ monotherapy caused repugnant autophagy suppression in metastatic pancreatic adenocarcinoma patients and exhibited minor therapeutic effectiveness [156]. In metastatic colorectal cancer patients, combining HCQ with histone deacetylase (HDAC) inhibitors, vorinostat or entinostat, did not improve the OS compared to standard treatment antiangiogenic tyrosine kinase inhibitor regorafenib [157,158]. Furthermore, employing HCQ to suppress autophagy in patients with advanced pancreatic cancer receiving gemcitabine and nab-paclitaxel had no meaningful effect on survival time, and the inclusion of HCQ in this therapeutic regimen has not been recommended without a biomarker [159]. Moreover, the co-administration of metformin and CLQ failed to provide a clinical effect in IDH-1- or IDH-2-mutated solid tumors [160]. CLQ monotherapy prior to surgery was likewise found not to affect breast cancer cell growth [161]. Inconsistent clinical results might be attributed to a lack of laboratory findings to identify appropriate individuals and poor information on resistance mechanisms. Furthermore, developing more potent autophagy inhibitors might help shed light on the precise position of autophagy in cancer treatment. Today, critical issues about the therapeutic utility of autophagy inhibitors in cancer appear to have gone unanswered, identifying the necessity for discovering the proper clinical recruitment of autophagy modulators in certain malignancies and stages of the disease. (Fig. 2).

4. Autophagy in GBM

Patients with GBM who receive existing accepted treatments have a poor prognosis, with an incidence rate of around 3.19 cases per 100,000 persons and a median overall survival (OS) rate of 14.6 months [172]. Notably, GBM tumor heterogeneity, angiogenic and highly infiltrative microenvironment, high mitotic activity, and cellular pleomorphism are associated with poor response to therapy. Thus, it is highly desirable to develop new treatment strategies that improve the current results [173].

As discussed earlier, autophagy is generally activated during cell growth to ensure an adequate food supply. Hence, autophagy is critical in maintaining cellular homeostasis, and as a result, it has been linked to the spread of cancer [174]. Even though autophagy has a regulatory function in both cell death and survival, the influence of autophagy on GBM throughout the stages of initiation, promotion, and progression is still debated [38]. An autophagic process has often been postulated as a tumor-inhibiting phenomenon by eliminating damaged proteins and organelles and protecting cancer cells against inflammation, genomic instability, and oxidative stress [175]. Nevertheless, it has been proposed that GBM cells activate autophagy in the presence of unfavorable conditions such as nutritional deprivation, acidosis, oxidative, or hypoxic stress to maintain their survival while avoiding the physiological response to disease and treatment [176]. Therefore, autophagy can potentially influence the prognosis of GBM, either favorably or adversely [177].

4.1. The impact of current GBM therapy on autophagy regulation

Conventional treatments for GBM include a combination of radiation therapy, chemotherapy, and surgical resection [178]. The alkylating drug temozolomide (TMZ) is the most often utilized chemotherapeutic agent for GBM chemotherapy [179]. It has been shown to cause apoptosis and senescence in tumor cells by directly damaging them through DNA methylation [180]. Additionally, TMZ serves as a radiosensitizer, raising the probability of radiation-induced DNA double-strand splits and cell death [181]. Despite the frequent administration of TMZ in primary and high-grade gliomas, treatment failure commonly occurs due to the development of tumor chemoresistance [38]. Regarding the literature, TMZ has been indicated to promote autophagy in GBM cells [182]. Although autophagy is a protective process, autophagic death is a mechanism to recruit the autophagic cargo to promote GBM cell apoptosis; accordingly, whether promoting protective or killing autophagy, TMZ therapy may precede chemoresistance or improve the apoptotic GBM cell death [183]. In terms of inducing autophagic death, overexpression of Beclin-1 in U87MG cells has been shown to stimulate apoptosis by binding to Bcl-2 and Bcl-xL, triggering cytochrome c release from the mitochondria and the intrinsic apoptotic pathway [184]. Reduced Beclin-1 and LC3-II expression were shown to promote GBM growth, providing proof of concept [185]. Likewise, silencing Beclin-1 and Atg5 abolished radiotherapy-induced apoptosis in various GBM cells [185]. In addition, autophagy promotion may induce senescence in GBM cells [186]. In line with these findings, provoking autophagy by TMZ-mediated modulation of the Akt/mTOR pathway and activation of AMPK/ULK-1 signaling was demonstrated to induce senescence and DNA damage in U87MG cells [187]. Consistently, autophagy suppression has abolished the impact of TMZ in preceding GBM cell senescence and apoptosis [188]. However, radiotherapy-mediated autophagic GBM cell death probably occurs independently of apoptosis through disabling the DNA repair [189–191].

On the other hand, autophagy plays a role in GBM development and chemoresistance. In malignant glioma, TGF-β1 induces autophagy, which triggers Smad2/3-astrocyte elevated gene 1 (AEG-1) signaling to recruit cyclin D1 oncogene and EMT factors to promote tumor development and invasion [192]. Furthermore, proteins involved in autophagy inhibit apoptotic GBM cell death. For instance, depleting ATG4C or silencing ATG9 has been demonstrated to promote ROS accumulation and suppress GBM proliferation and tumor progression [193,194]. In this regard, autophagy induction by TMZ promoted U87MG cell migration and infiltration, and knocking down Atg5 and Beclin-1 eliminated the impacts of TMZ [195]. ATG4C deficiency was also shown to suppress TMZ-mediated autophagy and enhance the sensitivity of GBM cells to TMZ [193]. Furthermore, Yuan et al. revealed that targeting ATG5 by specific siRNA or hindering autophagy by 3-methyladenine enhances the radiosensitizing impact of STAT3 inhibition in gliomas [196]. Consequently, depending on whether the protective autophagy or autophagic death mechanism is regulated, TMZ or radiation may cause contradictory effects in the treatment of GBM, and combing them with autophagy inhibitors or activators has been suggested to suppress GBM progression and prevent chemoresistance in a context-dependent fashion [38].

4.2. Natural products as autophagy modulators in GBM

Even though many chemotherapeutic drugs have been produced for cancer treatment in the modern era, the efficacy of a great deal of cancer medicine is still restricted or inadequate. Therefore, anticancer medications or techniques that can be used safely and effectively are urgently needed [197]. In recent decades, several naturally occurring products with clear evidence of anticancer action have been identified [5]. Generally, the study of herbals is an effective method for finding physiologically active compounds with distinct structures and mechanisms [198]. In light of the incredible variety seen in the natural world, it is possible to discover chemical leads capable of interacting with most therapeutic targets [199]. Currently, natural products like taxol,

vinblastine, and camptothecin constitute a large fraction of pharmacological agents with novel modes of action, most notably in the field of cancer treatment [7,200–202]. Notably, the ability of phytochemicals to alter autophagy should be considered while developing new therapies. Interestingly, autophagy may be modulated by dietary components such as resveratrol, berberine, quercetin, and curcumin through affecting canonical (Beclin-1-dependent) and noncanonical (Beclin-1-independent) pathways [203,204]. In the following, the function of autophagy in the anti-GBM actions of these compounds is addressed.

Curcumin, also known as diferuloylmethane, is an active component of the spice turmeric, which comes from the plant *Curcuma longa* [205]. Curcumin is a multifunctional phytochemical with numerous biological and pharmacological activities [206–213]. This component has a powerful anti-cancer impact on cancer cells [214–218]. The PI3K/Akt/mTOR signaling pathway and NF-κB-regulated proteins are the primary targets of its action [219]. Curcumin was shown to cause G2/M arrest and autophagy in malignant GBM cells by suppressing the Akt/mTOR/p70S6K pathway and activating the ERK1/2 signaling, suggesting that cell death through autophagy may be pathway-specific [215]. Furthermore, it was shown that curcumin's anticancer properties are linked to the stimulation of autophagy in A172 GBM cells through the enhanced expression of Atg5 and Beclin-1 [220]. Curcumin also dramatically suppressed the development of a xenograft GBM model via triggering autophagy [221]. These findings lend credence to the hypothesis that autophagy induction is required for the antitumor activity of curcumin. In this regard, Shinojima and colleagues showed that NF-κB suppression does not play a substantial role in the death of malignant GBM cells, and autophagy is the primary mechanism responsible for the anti-cancer effects [222]. Another study evaluated the autophagic responses of U87MG, GL261, F98, C6, and N2a cells following treatment with curcumin or a novel solid lipid curcumin particle (SLCP) (25 μM for 24 h). SLCP demonstrated a more significant disruption of the PI3K/Akt/mTOR signaling pathway than curcumin. This was accompanied by more robust autophagy activation and greater mitophagy marker suppression, suggesting that treatment with SLCP to limit GBM cell growth and proliferation may have promised therapeutic applications [223]. Likewise, Bagherian et al. found that nanomicellar curcumin formulation at a concentration of 50 μM combined with TMZ had the most significant inducing effect on the expression levels of autophagy-related proteins (e.g., Beclin-1 and LC3-II) [224]. Besides, the anti-migration and anti-invasion properties of curcumin nanocarriers on A172 cells have been shown by Zhang et al., curcumin/LDH NPs remarkably induced Atg5, Atg12, and lysosomal-associated membrane protein-1 (LAMP-1) expression and enhanced the formation of the autophagic vacuole, indicating that autophagy may participate in the anti-migration and anti-invasion actions of curcumin/LDH NPs against GBM [225].

As a cancer therapeutic agent and autophagy mediator, the flavonoid quercetin is found in various foods such as fruits and vegetables [226]. The cytotoxic effect of anticancer drugs may be increased by effectively controlling autophagy, but how to do so in a way that generates an excellent therapeutic effect on GBM remains unknown [227]. In this respect, Kim et al. have found that quercetin induced autophagy in U373 GBM cells and recruiting CLQ, an approved autophagy inhibitor, caused significant apoptosis induction, underlying the impact of quercetin in provoking protective autophagy in these cells [228]. In another study, quercetin reduced cell survival and activated autophagy of U87MG and U251 GBM cells in a dose-dependent manner. Then, 3-methyl adenine (3-MA) and Beclin-1 small hairpin RNA (shRNA) were used to block the early stage of autophagy, and a reduction in the cytotoxicity of quercetin was observed. The suppression of autophagy at a late stage by CLQ, on the other hand, increased the effectiveness of quercetin against GBM. Therefore, the therapeutic impact of quercetin for malignant GBM may be increased by inhibiting autophagy at a late stage, as opposed to an early stage, which may present a fresh option for the treatment of GBM [229]. Recent research has shown that recruiting nanocarriers increases drugs' effectiveness and decreases their unwanted side effects [230,231]. In this regard, Lou et al. have investigated the impact of gold-quercetin incorporated into poly (dl-lactide-co-glycolide) nanoparticles (NPs) on GBM cells. Upon treatment with quercetin NPs, the function of PI3K/Akt signaling and the expression of Bcl-2 was downregulated in human neuroglioma cells. There was a clear correlation between the amount of quercetin NPs and the levels of LC3, ERK, cytoplasmic p53, cleaved caspase-3, and poly (ADP-ribose) polymerase (PARP). In addition, a dose-dependent reduction in p-mTOR and Galpha-interacting protein (GAIP) expression was seen after treatment with quercetin NPs. According to these findings, quercetin NPs may activate LC3/ERK/caspase-3 and inactivate Akt/mTOR signaling in human neuroglioma cells, leading to autophagy and death [232]. Furthermore, quercetin has been used in conjunction with other well-established cancer treatments to achieve synergistic therapeutic results. As an example, Taylor et al. evaluated the effectiveness of quercetin in conjunction with sodium butyrate (NaB) in provoking death in rat C6 and human T98G cells by blocking autophagy during nutrient starvation. The drug concentrations that created the highest level of synergy in both cell lines were 25 μM quercetin and 1 mM NaB. When autophagy was quantified by acridine orange staining, quercetin or quercetin plus NaB treatment caused significant suppression of protective autophagy (i.e., decreased Beclin-1 and LC3B II expression) in the cells that were deprived of nutrients. Furthermore, the results of the Western blot demonstrated that the combination of quercetin and NaB enhanced apoptosis by lowering Bcl-2 and raising Bax, as well as by reducing survivin levels, activating caspase-3, and degrading PARP. In a nutshell, the therapeutic potentials of the innovative combination treatment for blocking protective autophagy to promote apoptosis in rat C6 and human T98G GBM cells were established [233]. Quercetin has also been demonstrated to enhance the cytotoxic impact of t-AUCB (a soluble epoxide hydrolase inhibitor) against GBM cells by reducing the expression of HSP27 and its downstream Atg7 and inhibiting autophagy [234,235]. Of note, HSP27 is an essential regulator of cancer growth, progression, metastasis, and chemoresistance [236].

Berberine, an isoquinoline alkaloid discovered from Berberis vulgaris L., has been used to a significant degree in treating diarrhea and diabetes in traditional Chinese medicine [237,238]. Recent research has demonstrated that berberine has the ability to inhibit the growth of several different cancer cell types, including ovarian, colorectal, lung, prostate, and especially GBM [239,240]. It has been revealed that berberine (0–200 μM) might significantly affect the metabolic status of GBM cells (e.g., U251, and U87MG) through the suppression of the AMPK/mTOR/ Unc-51 like autophagy activating kinase-1 (ULK-1) pathway, resulting in increased autophagic flux and reduced glycolytic ability. The functional effects of these modifications include a diminution of invasive capabilities, a reduction in the capacity for cell proliferation, and the induction of apoptotic cell death [241]. Because of the development of therapeutic resistance, the use of TMZ for GBM treatment has been hindered. In this regard, TMZ-resistant GBM cell lines were employed to evaluate the berberine capacity to change TMZ resistance. Berberine has been shown to increase the sensitivity of GBM cells to TMZ treatment in a way that is reliant on the ERK1/2-mediated activation of autophagy, making it a potential therapeutic agent for GBM therapy [242].

According to the literature, cucurbitacin I, a naturally occurring selective inhibitor of JAK2/STAT3, has recently been considered a potent antitumor agent in diverse kinds of cancer cells [243]. Yuan and colleagues found that treating T98G and U251 cells with cucurbitacin I led to apoptosis and autophagy as indicated by Bcl-2 family proteins and Beclin-1 upregulation, autophagosome formation and accumulation, and increased LC3-II/I ratio. Furthermore, activation of AMPK/mTOR/p70S6K signaling and reduced hypoxia-inducible factor 1 (HIF-1α) expression were observed. Inducing the expression of HIF-1α by FG-4497, silencing Beclin-1, or administration of 3-MA reversed cucurbitacin I-mediated autophagy. Notably, recruiting CLQ or

Table 2
Potential natural compounds targeting autophagy in GBM cells.

Natural product	Type of study	Dose of administration	Pharmacological finding (s)	Reference
Amentoflavone	*In vitro*	0–20 μM	– Promoted autophagy by regulating autophagy-relevant proteins Atg5, Atg7, Beclin-1, and LC3BII, through regulation of AMPK/mTOR signaling.	[249]
Omega3-polyunsaturated fatty acids (ω3-PUFAs)	*In vitro*	0–50 μM	– Elevated autophagic activity, as shown by enhanced LC3-II levels, GFP-LC3 puncta, and autophagic flux activation, accompanied by activating AMPK and decreasing phosphorylated Akt levels as well as mTOR activity.	[250]
4-Hydroxy tamoxifen (OHT)	*In vitro*	3–12 μM	– Induced both cytotoxic autophagy and a concentration-dependent reduction in EGFR protein levels.	[251]
Honokiol	*In vitro*	0–50 μM	– Increased markers of autophagy such as Beclin-1 and LC3–II.	[252]
Galangin	*In vitro*	0–400 μM	– Increased autophagy as well as the formation of autophagic vesicles – Suppression of autophagy improved Galangin-mediated apoptosis and pyroptosis in GBM cells.	[253]
Coibamide A	*In vitro*	0–300 nM	– Induced autophagosome accumulation via an mTOR-independent mechanism.	[254]
Resveratrol	*In vitro*	37.5–300 μM	– Induced autophagy. – Autophagy suppressed resveratrol-induced apoptosis. – Increased protein levels of Beclin-1 and LC3-II. – Autophagy inhibitors 3-MA and bafilomycin A1 potentiated the cytotoxicity of resveratrol.	[255]
Thymoquinone	*In vitro*	0–35 μM	– Inhibited autophagy by an accumulation of the LC3-associated protein p62. – Triggered cathepsin-induced, caspase-independent cell death.	[256]
Silibinin	*In vitro*	0–250 μM	– Induced autophagy through upregulation of LC3-II. – Induced apoptosis concomitant with autophagy through simultaneous inhibition of mTOR and YAP.	[257]
AKBA[a]	*In vitro* *In vivo*	10–30 μM 100 mg/kg	– Repressed the expression of Atg5, p62, LC3B, p-ERK/ERK, and P53 and elevated the ratio of p-mTOR/mTOR.	[258]
Euphol	*In vitro*	8 and 30 μM	– Increased the development of AVOs, which is possibly associated with autophagy.	[259]
Ganoderic acid A	*In vitro*	0–50 mg/ml	– Augmented the levels of two autophagy markers (Beclin-1 and LC3 II), inducing autophagy.	[260]
Peiminine	*In vitro*	100, 200, and 400 μM	– Suppressed the autophagic flux by depressing AMPK-ULK-1 signaling.	[261]
Verbascoside	*In vitro*	50 μM	– Promoted cell apoptosis and autophagy through inhibiting the HMGA2 and Wnt/β-catenin signaling pathways.	[262]
Diosmin	*In vitro*	250 μM	– Increased the expression of LC3-II and p62, inhibiting autophagic flux.	[263]
Luteolin	*In vitro*	0–30 μM	– Elevated the expression levels of LC3B II/I and reduced the level of p62 that promotes cell autophagy.	[264]

Abbreviations: AMPK; AMP-activated protein kinase, mTOR; Mammalian target of rapamycin, EGFR; Epidermal growth factor receptor, 3-MA; 3-methyl adenine, AVO; Acidic vesicular organelle, ERK; Extracellular signal-regulated kinase

[a] 3-O-Acetyl-11-keto-β-boswellic acid

knocking down Beclin-1 improved the apoptotic cell death induced by cucurbitacin I, indicating its role in provoking protective autophagy in GBM cells. These findings provide fresh light on the molecular pathways responsible for cucurbitacin I to modulate GBM autophagy and suggest the possibility of an effective treatment for individuals who are afflicted with GBM [176].

Antiapoptotic members of the Bcl-2 family decrease apoptosis as well as autophagy, and they play a significant role in the therapeutic resistance of malignant GBM [244]. Gossypol, a natural polyphenolic BH3-mimetic Bcl-2 inhibitor, shows promise as a potential treatment for solid tumors [245]. Voss et al. have demonstrated that in apoptosis-resistant malignant GBM cells, gossypol promotes caspase-independent, autophagic cell death and enhances TMZ activity [246]. Additionally, Kim et al. have demonstrated that gossypol therapy for DBTRG-05MG cells stimulated autophagy, as indicated by increased GFP-LC3-positive cells and increased LC3II expression. Importantly, these cells showed reduced sensitivity to gossypol cytotoxicity when treated with 3-MA, indicating that gossypol-induced growth inhibition is largely mediated by autophagy [247]. According to the findings of another research, the addition of gossypol to irradiated GBM cells resulted in a considerable increase in the accumulation of acidic vesicular organelles (AVO). This suggests that gossypol is a potential medication that induces autophagic cell death in radioresistant malignant GBM [248]. Other potential natural products affecting autophagy in GBM are listed in Table 2.

4.3. Potential chemical compounds affecting autophagy in GBM

4.3.1. HDAC inhibitors

Histone deacetylase (HDAC) inhibitors like vorinostat, belinostat, panobinostat, romidepsin, and chidamide, are emerging as a novel class of therapeutic medicines with favorable effects in the treatment of a broad variety of malignancies [265]. Hematological cancers tend to be especially responsive to HDAC inhibitors; nevertheless, a variety of new cancer types are now being studied to determine their susceptibility to HDAC inhibitor treatment [266]. The FDA has approved vorinostat (suberoylanilide hydroxamic acid; SAHA) as the first drug of HDAC inhibitors for the treatment of cutaneous T-cell lymphoma, which suppresses HDACs 1, 2, 3, and 6 [267]. In cancer cells, SAHA has been shown to induce apoptosis, growth arrest, and polyploidy, all of which are associated with its anticancer actions. HDAC inhibition has also been demonstrated to activate autophagy in more recent studies [268]. It is noteworthy that vorinostat (0–20 μM) promotes the expression of the autophagic protein LC3 and inhibits mTOR, both of which are important for cell survival. The dephosphorylation and subsequent activation of the autophagic protein kinase Atg1, which is required for autophagy activation following vorinostat therapy, also happened as a result of the inhibition of mTOR activity. In GBM cells (T98G), RNAi has been demonstrated to accelerate vorinostat-induced apoptosis by inhibiting autophagy. Vorinostat-induced non-apoptotic cell death may also be enhanced when apoptosis is pharmacologically inhibited. To summarize, vorinostat activates autophagy by inhibiting mTOR and upregulating LC3 expression; autophagy works as a prosurvival mechanism to attenuate vorinostat-induced apoptotic and non-apoptotic cell death, indicating that inhibiting autophagy may enhance the therapeutic benefits of vorinostat [269]. Vorinostat (0–20 μM) has also been shown to reduce survival and induce apoptosis in the late phases of GBM stem cells (GSCs) in vitro and suppress tumor growth in xenografted animal models. In addition, vorinostat triggered autophagy by increasing intracellular AVO production, recruiting LC3-II to autophagosomes, elevating the protein concentration of Beclin-1, and decreasing the concentration of SQSTM1. Furthermore, vorinostat was discovered to

Table 3
Potential chemical agents are affecting autophagy in GBM.

Chemical agent	Type of study	Main finding (s)	Reference
Itraconazole	In vitro and in vivo	– Inducing autophagic progression. – Itraconazole's antiproliferative properties are dramatically reversed when autophagy is blocked, indicating that autophagy may have an anticancer impact in response to itraconazole therapy. – It has been shown that Itraconazole inhibited cell proliferation by repressing Akt1-MTOR signaling, inducing autophagy, and lowering the levels of SCP2 in late endosomes and lysosomes.	[275]
Chlorpromazine	In vitro	– Induces cytotoxic autophagy via endoplasmic reticulum stress and unfolded protein response.	[276]
Regorafenib	In vitro and in vivo	– Regorafenib induces autophagosome accumulation in GBM cells by driving autophagy initiation and blocking autophagosome-lysosome fusion. – Regorafenib inhibits GBM cell growth by promoting autophagosome accumulation.	[277]
Melatonin	In vitro	– Induced autophagy.	[278]
FTY720[a]	In vitro and in vivo	– Induced extrinsic apoptosis, necroptosis, and autophagy.	[279]
Nitazoxanide	In vitro	– Inhibited autophagy through blockage of late-stage lysosome acidification.	[280]
Pimozide	In vitro	– An upregulation of LC3B, Beclin-1, and Atg5, inducing autophagy.	[281]
Thioridazine	In vitro	– Induces autophagy by upregulating AMPK activity. – Enhancing P62-mediated autophagy and apoptosis through Wnt/β-catenin signaling.	[282]
Dapivirine	In vitro	– A reduction in LC3A/B-I and the ratio of LC3A/B-II to LC3A/B-I were increased. – The expression of Atg7 and Beclin-1 was increased, inducing autophagy.	[283]
Ivermectin	In vitro	– Induced autophagy through Akt/mTOR signaling.	[284]

Abbreviations: GBM; Glioblastoma multiforme, AMPK: AMP-activated protein kinase, mTOR; Mammalian target of rapamycin
[a] a potent immunosuppressant

induce autophagy via downregulating Akt/mTOR signaling, which is a primary inhibitory cascade of autophagy. This suggests that vorinostat-mediated induction of autophagy may serve as a prosurvival mechanism since when autophagy is inhibited or depleted, vorinostat promotes apoptosis and causes cell death in the early phases. Another interesting finding of this study was the synergistic impact of CLQ on apoptosis through inhibiting vorinostat-induced protective autophagy. To put it another way, the findings suggest that vorinostat might be a potential drug for targeting GSCs through the induction of autophagy [270]. In accordance with these findings, a clinical study by Galanis et al. found that vorinostat monotherapy was well tolerated and had limited efficacy in patients with recurrent GBM. Vorinostat has been shown to influence GBM target pathways by evaluating histone acetylation and RNA expression profiling, although more drug testing in combination regimens is needed [271].

Interestingly, Gonçalves et al. recently tested the effectiveness of combining TMZ with vorinostat in vitro and in vivo in GBM models. The combination of TMZ and vorinostat resulted in more cytotoxicity, G2/M arrest, and apoptosis than either medication alone. It was shown that TMZ and vorinostat, either alone or in combination, activated autophagy, as demonstrated by acridine orange staining and immunodetection for the conversion of LC3-I/II and degradation of p62/SQSTM1. Autophagy was associated with G2/M arrest and apoptosis, and blocking the late phases of autophagy with CLQ increased vorinostat/TMZ toxicity, which resulted in apoptosis [272]. N25, a new inhibitor of HDAC, was produced by structurally altering the vorinostat. The antiproliferative and anticancer effects of N25 (0–25 μM) on GBM cells (U87MG and U251 cells) were examined by Sun et al. *In vitro* and in vivo experiments were conducted to determine if it has antitumor action and to clarify the molecular mechanism by which it induces autophagy [273]. Both in vitro and in vivo, the antitumor activity of N25 in GBM cells was shown to be slightly more significant than that of vorinostat. Pharmacologically, autophagy was enhanced in GBM cells following treatment with N25 by suppressing HDAC3 and upregulating the protein expression of Tip60, Atg1, and Atg6 [274]. Other potential chemical compounds have been listed in Table 3.

4.3.2. Nanoparticles

Nanotechnology has brought new capabilities for treating human cancers. Due to their unique physical and chemical qualities, nanoparticles (NPs) can be employed to create novel anticancer medicines with improved pharmacokinetics and pharmacodynamics [43]. NPs, formed from inorganic, polymeric, or organic materials, are tiny structures having a diameter between 1 and 100 nm that can be loaded with medications [231]. Certain kinds of NPs have originated so far to possess anticancer properties through autophagy modulating [230]. *In vitro* and in vivo assessments in glioma models revealed that silver NPs (AgNPs) exhibit antitumor and radiosensitizing effects in a size and dose-dependent manner. The 2 nm AgNPs showed greater toxicity than 15 nm NPs at the same concentrations against U251 cells, while 40 nm AgNPs showed no cytotoxicity even at higher concentrations. Furthermore, exposing to a 0.1 mM concentration of 15 nm AgNPs for 24 h significantly enhanced the cytotoxic impact of a 4 Gy irradiation through promoting necrosis and apoptosis. The authors revealed that AgNPs or AgNPs plus irradiation provoked protective autophagy in U251 cells through triggering ERK and JNK signaling as indicated by increasing LC3-II expression and P62 degradation, which was reversed by the application of autophagy inhibitor, 3-MA, or specific ERK and JNK inhibitor, SP600125. The application of 3-MA remarkably enhanced the apoptosis rate and improved the outcome of AgNPs associated-radiotherapy [285]. To clarify the mechanism underlying the radiosensitizing impact of AgNPs, the same research team recruited antioxidants to regulate ROS in U251 cells treated by 15 nm AgNPs or AgNPs plus 4 Gy irradiation. *In vitro* assessments revealed that AgNPs at 0.1 mM concentration caused a 3-fold increase in ROS generation, impaired mitochondrial membrane potential (MMP), and reduced the viability of U251 cells. Notably, the elevated ROS generation and apoptosis in cells exposed to AgNPs and irradiation were inverted by n-acetylcysteine (NAC), underscoring the role of ROS in AgNPs' radiosensitizing impact. More interestingly, pretreatment with antioxidants reversed the LC3-II elevation induced by AgNPs or AgNPs plus irradiation, indicating that autophagy is downstream of ROS. It has been confirmed that autophagy triggered by ROS could repress cellular ROS generation and defend cells from ROS-mediated apoptosis. As a proof of concept, inhibition of autophagy by 3-MA increased ROS generation, elevated caspase-3 expression, and promoted apoptotic cell death. The obtained results showed that ROS plays a fundamental role in inducing autophagy and the radiosensitizing effect of AgNPs [286,287].

Moreover, AgNPs were demonstrated to be nontoxic in normal cells while showing dose-dependent cytotoxic impact in U251 cells and promoted irradiation-mediated apoptosis. The combination of AgNPs and radiation therapy also caused more significant levels of autophagy than that of AgNPs alone, as indicated by increased LC3-II protein expression as well as acridine orange and monodansylcadaverine (MDC) staining. The authors argued that this type of autophagy is protective,

and its inhibition may improve the radiosensitizing impacts of AgNPs [288]. An intriguing study by Liu et al. showed that AgNPs with an average size of about 27 nm enhanced irradiation-induced MMP impairment and apoptosis in a dose-dependent way with more significant effects in hypoxic rather than normoxic U251 cells. Using the green fluorescent probe Cyto-ID, AgNPs were shown to increase irradiation-induced autophagy. Interestingly, recruiting 3-MA nullified the cytotoxicity of combination therapy in hypoxic cells while promoting cytotoxicity in normoxic cells, displaying the role of AgNPs and irradiation in provoking destructive autophagy and eradicating hypoxic cells [289].

Several additional research studies have shown that silica NPs (SiNPs) have a lethal impact on cancer cells by influencing the autophagy process [290,291]. SiNPs are widely employed in various medicinal applications, but the mechanisms through which they might be toxic are unknown [292]. A study by Krętowski showed that in LBC3 glioblastoma cells, SiNPs (5–15 nm) dose-dependently triggered oxidative stress, impaired MMPS, upregulated proapoptotic proteins (e.g., *Bax* and *Puma*), and increased caspase-9 activity, promoting apoptosis. Furthermore, these NPs induced autophagy, as indicated by an increase in the LC3-II/I ratio, the overexpression of Atg5, and an increase in the number of AVOs-positive cells. Whether this type of autophagy contributes to apoptosis induction or protects cells against apoptotic insults remains unclear and is needed to be determined by recruiting an autophagy inhibitor [293].

As NPs have become more popular, they have been able to overcome the restrictions of conventional treatments. In addition to their direct effects on autophagy regulation, engineered NPs have been recruited for safe and effective delivery of drugs modulating autophagy at the tumor site. For instance, novel polyethylene glycol-dipalmitoylphosphatidylethanoiamine (mPEG-DPPE) calcium phosphate NPs have been designed for sustained local delivery of paclitaxel (PTX) and TMZ to glioma tumors. These NPs have a particle size of about 38 nm and a negative surface potential desirable for long circulation time and accumulation in the tumor vasculature. PTX-TMZ NPs induced autophagy as indicated by green MDC puncta, increased LC3-II/I ratio, SQSTM1 degradation, and autophagosome formation. Interestingly, these NPs were shown to regulate cancer cell death by inducing antiproliferative autophagy in C6 glioma cells since autophagy inhibition inverted the antitumor impact of PTX-TMZ NPs. Moreover, PTX-TMZ NPs were loaded into a thermoresponsive gel with the capability of injecting into a tumor resection cavity and maintaining a therapeutic concentration of PTX and TMZ. The nanosystem was assessed in C6 tumor-bearing rats and showed significant anti-tumor effects [294]. Iron oxide nanoparticles loaded with PTX (IONP@PTX) have also been introduced as potential tools for fighting cancer. Examination of these NPs on U251 cells revealed more significant inhibitory effects than that of PTX alone. IONP@PTX attenuated cell migration, induced oxidative stress, increased the expression of autophagy-related proteins, e.g., Beclin-1 and LC3-II, and downregulated p62 and ferroptosis-related protein GPX4 in vitro. These NPs also reduced tumor volume and GPX4 expression in GBM xenografts. Notably, 3-MA or rapamycin administration nullified the tumor suppressive impact of IONP@PTX in vivo and in vitro, demonstrating the outstanding effect of autophagy-dependent ferroptosis in GBM cell death [295]. Additionally, it has been shown that the process of autophagy may be upregulated in GBM cells by ultrasmall IONPs, also known as USIONPs. Wen and colleagues discovered that USIONPs increase the expression of ferroptosis markers in GBM cells while simultaneously decreasing the expression of anti-ferroptosis genes. In the meanwhile, the autophagy inhibitor 3-MA was able to reverse the ferroptosis that was produced by USIONPs. In addition, the overexpression of Beclin-1/Atg5 in the autophagy process could considerably accelerate USIONPs-induced ferroptosis, while shRNA suppression of upstream genes of the autophagy process could significantly reverse USIONPs-induced ferroptosis. The accumulation of these observations leads one to conclude that USIONPs-induced ferroptosis is controlled by an autophagy mechanism that depends on Beclin-1/Atg5 [296].

Table 4
Potential combining regimen approaches targeting autophagy in GBM.

Combination regimen	Type of study	Main finding (s)	Reference
Hydroxychloroquine + Bevacizumab	In vitro	– Inhibition of autophagy.	[301]
Thioridazine + Temozolomide	In vitro	– Inhibits autophagy and sensitizes GBM cells to TMZ.	[302]
Momelotinib + Temozolomide	In vitro In vivo	– Activating both apoptosis and autophagy pathways. – Increased ratio of LC3–II/I and the expression of caspase-3 and Beclin-1.	[303]
Lovastatin + Temozolomide	In vitro	– Enhances cytotoxicity of TMZ via impairing autophagic flux.	[304]
Acteoside + Temozolomide	In vitro	– Increased LC3 and apoptosis-related gene expression. – Induced apoptosis and autophagy through the MAPK signaling pathway.	[305]

Abbreviations: GBM; Glioblastoma multiforme, TMZ; Temozolomide, LC3; Microtubule-associated protein 1 light chain 3, MAPK; Mitogen-activated protein kinase.

Although, the enormous task in the next several years will be to overcome the flaws in these new techniques and finally encourage the translation of medicines. In this perspective, even if it is possible to develop highly novel and complicated supermolecular NPs, using simplicity and biomimicry in the design of NPs seems to be more effective when considering scale-up and clinical applications.

5. Concluding remarks and future directions

Since autophagy and its link to cancer were discovered, there has been a lot of discussion about the best possible way to use its contradictory characteristics. Numerous studies have shown that autophagy is a crucial component of mammalian growth and vital to their continuing existence. Autophagy is a well-preserved evolutionary response that destroys and recycles cellular components to maintain homeostasis [297]. Nevertheless, if cells are exposed to harmful stimuli such as insufficient nutrition, ROS, low oxygen levels, or cancer-causing stimuli, they will activate autophagy as a defensive mechanism to maintain their survival. Protective autophagy enables the destruction and subsequent recycling of proteins and organelles that are not essential for life. This includes proteins that are crucial for inducing apoptosis. On the other hand, excessive autophagy induction might result in an increase in the amount of cellular breakdown, which can eventually trigger autophagic cell death. Some researchers assume that excessive autophagy might cause a different kind of cell death called synergistic cell death, which works in conjunction with apoptosis. A significant number of researchers maintain that it is preferable to suppress protective autophagy to render inherently chemo-resistant tumors like GBM relatively amenable to treatment [298].

GBM is one of the most challenging neoplasms to treat because of its heterogeneity, complex TME, and invasiveness. In addition, GBM may include glioma stem cells, which can proliferate at a high rate and have the ability to renew themselves, making them a significant contributor to the development of the tumor and its resistance to treatment. Furthermore, a high concentration of antiapoptotic proteins and low expression of proapoptotic proteins in GBM may contribute to the activation of oncogenes and the development of genetic instability, both of which increase tumor survival and the ability to withstand treatment with radiation, chemotherapy, and immune therapy. On the other hand,

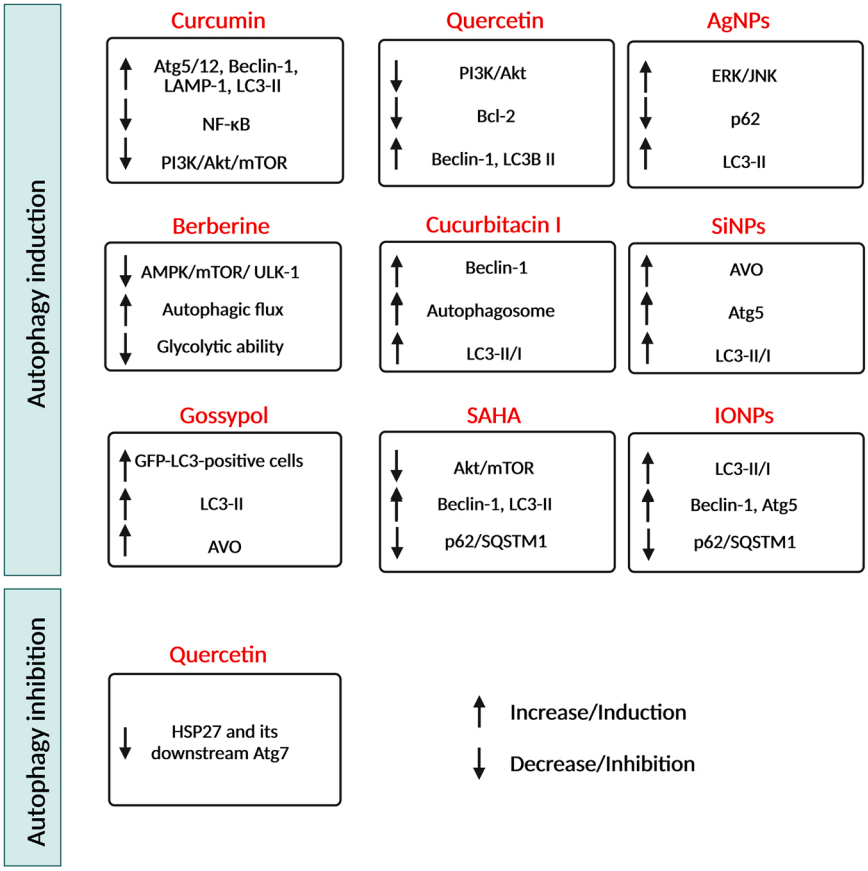

Fig. 3. Suggested mechanisms for natural and chemical compounds in regulating GBM autophagy. **Abbreviations:** Atg; Autophagy-related, LAMP-1; Lysosomal associated membrane protein 1, LC3; Microtubule-associated protein 1 light chain 3, NF-κB; Nuclear factor kappa B, PI3K; Phosphoinositide 3-kinase, Akt; Protein kinase B, mTOR; Mammalian target of rapamycin, ERK; Extracellular signal-regulated kinase, JNK; c-Jun N-terminal Kinase, AMPK; AMP-activated protein kinase, ULK-1; Unc-51 like autophagy activating kinase, AVO; Acidic vesicular organelles, SQSTM1; Sequestosome 1, HSP; Heat shock protein.

the process of cell death characterized as autophagy, has recently gained attraction as a potentially helpful method for eliminating neoplastic cells. Autophagy modulators have been used to halt cancer growth due to manipulating the autophagic process as a death mechanism in neoplasms. Since GBM is a distinct kind of cancer that may manifest in various ways leading to death, it has been challenging to develop an effective therapy for the disease. This underscores how important it is to continue research on autophagy to make this mechanism relevant to the treatment of GBM [299]. Some potential autophagy modulators are being studied in preclinical studies with chemotherapy medications to see whether they might improve the effectiveness and therapeutic outcomes (Table 4). However, there have been only a few autophagy promoters and inhibitors tested in clinical studies concerning autophagy regulation. In addition, there is a lack of consistency in the outcomes regarding the improvement of patient survival. For many patients with GBM, a better prognosis may be achieved by using autophagy as a complement to existing and innovative treatments, which may reduce the chemoresistance and radioresistance found in GBM [300]. In addition, even though the successful treatment of the disease remains as a formidable obstacle, another noteworthy and promising finding was the possibility that rationally designed NPs might help improving the survival of patients with GBM through inhibition of autophagy flux and prevention of damaged DNA repair of tumor cells. The mechanism of natural and chemical compounds in regulating GBM autophagy are summarized in Fig. 3. More studies are required to assess the anticancer effectiveness of therapies for GBM that incorporate autophagy modulators in addition to chemotherapeutic medicines. Finally, there is a need for more research to be carried out to create effective cancer-specific delivery methods and medications, which will make tumors more receptive to therapies.

CRediT authorship contribution statement

Conceptualization: MS, ARA, AS Writing-original draft: MS, MMB, SSA Writing-review and editing: SA, HJ, HM, BB, EM, TJ, ARA, AS Approval of the final version: All authors.

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