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Advances in mitophagy and mitochondrial apoptosis pathway-related drugs in glioblastoma treatment

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Glioblastoma (GBM) is the most common malignant tumor of the central nervous system (CNS). It is a leading cause of death among patients with intracranial malignant tumors. GBM exhibits intra- and inter-tumor heterogeneity, leading to drug resistance and eventual tumor recurrence. Conventional treatments for GBM include maximum surgical resection of glioma tissue, temozolomide administration, and radiotherapy, but these methods do not effectively halt cancer progression. Therefore, development of novel methods for the treatment of GBM and identification of new therapeutic targets are urgently required. In recent years, studies have shown that drugs related to mitophagy and mitochondrial apoptosis pathways can promote the death of glioblastoma cells by inducing mitochondrial damage, impairing adenosine triphosphate (ATP) synthesis, and depleting large amounts of ATP. Some studies have also shown that modern nano-drug delivery technology targeting mitochondria can achieve better drug release and deeper tissue penetration, suggesting that mitochondria could be a new target for intervention and therapy. The combination of drugs targeting mitochondrial apoptosis and autophagy pathways with nanotechnology is a promising novel approach for treating GBM.This article reviews the current status of drug therapy for GBM, drugs targeting mitophagy and mitochondrial apoptosis pathways, the potential of mitochondria as a new target for GBM treatment, the latest developments pertaining to GBM treatment, and promising directions for future research.

KEYWORDS

drugs, glioblastoma, mitochondrial apoptosis, mitophagy, new developments

1 Introduction

Glioblastoma (GBM) is a malignant tumor that develops from astrocytes, which are cells that support nerve cells in the brain(Watson et al., 2023). It can also develop from mutations in specific pathways related to cell death and proliferation in different cells of the brain(Louis et al., 2021). Unfortunately, it has the lowest 5-year relative survival rate among central nervous system tumors (6.8%) (Ostrom et al., 2019). The first-line treatment for GBM includes maximal surgical resection followed by concomitant chemoradiotherapy and adjuvant chemotherapy (TMZ). (Szklener et al., 2022). After standard-of-care surgery and adjuvant chemotherapy, the approximate median survival is 14–16 months. It is mainly induced by its high resistance to radiotherapy and chemotherapy and the inability to remove the tumor tissue completely (Ohgaki and Kleihues, 2005; Lah et al., 2020). GBM-initiating cells (GICs), also known as GBM stem cells (GSCs), have the potential for self-renewal, multi-directional differentiation, and tumor initiation,

TABLE 1 Summary of main mitophagy and mitochondrial apoptosis pathway-related drugs in GBM treatment.

Classification	Drugs
Mitophagy pathway-related drugs	Silibinin
	Cannabidiol
	Gossypol (AT-101)
Apoptosis pathway-related drugs	Xanthohumol
	Pterostilbene
	Chrysophanol
	Shikonin
	Grape seeds
Mitophagy and mitochondrial apoptosis pathway-related drugs	Sinomenine

which are associated with treatment resistance and relapse and are considered to be the cause of relapse in most patients with this devastating disease (He et al., 2021; Yi et al., 2019, Osuka and Van Meir, 2017). Temozolomide (TMZ) is a currently the first-line drug used for GBM treatment independent of the methylation state of O6-methylguanine methyltransferase(MGMT), which can induce DNA strand breaks during cell replication and thus promotes cell apoptosis(Hegi et al., 2019). Owing to the overexpression of MGMT and the lack of DNA repair pathways in GMB, TMZ-resistance is a major obstacle in improving the prognosis of patients with GBM (Chen et al., 2018; Lin et al., 2022a). Furthermore, phenotypic and genotypic heterogeneity (Banelli et al., 2017), hypoxic tumor environment (Ho et al., 2022), the presence of glioblastoma stem cells (Huang et al., 2020), abnormal signaling pathways (Yu et al., 2019; Liu et al., 2020a; Lee et al., 2022a), and notably, the existence of the blood–brain barrier (BBB) (Zou et al., 2022) result in a need for increased chemotherapeutic drug doses to reach effective concentrations of the drugs, which worsens the systemic side effects of the drugs (Oberoi et al., 2016). Therefore, further research, drug development, and identification of novel and effective drugs are urgently needed.

In recent years, natural products, synthetic drugs, and cytokines targeting the mitochondria have increasingly been applied for the prevention and treatment of various tumors, and their promising results in anti-tumor research and application are becoming evident. This review focuses on research progress into potential natural drug leads for inducing mitophagy or apoptotic pathways that may be relevant to GBM (Tab.1).

2 Mitophagy and GBM

2.1 Mitophagy

Mitochondria are important organelles that play important roles in cellular metabolism, including but not limited to the production of ATP via electron transport coupled with oxidative phosphorylation, tricarboxylic acid cycle, fatty acid β-oxidation, amino acid synthesis, calcium homeostasis, and iron metabolism (biosynthesis of heme and iron-sulfur clusters) (Zhang et al., 2022a). According to the International Cancer Genome Consortium and The Cancer Genome Atlas Program, mutations in mitochondrial DNA (mtDNA) can be detected in approximately 60% of solid tumors, and the accumulation of mutations in mtDNA can result in mitochondrial dysfunction(Leao et al., 2021). In glioma, mitochondrial function is impaired by marked alterations in the mitochondrial genome, resulting in altered morphology and abnormal bioenergetics, including increased ROS production(Lu and Ho, 2020). Mitochondrial dysfunction plays a crucial role in the regulation of several cancer intrinsic pathways related to tumor metabolism, survival, proliferation, and cell death in GBM (Lu and Ho, 2020).

Autophagy, morphologically characterized by the formation of autophagosomes or autolysosomes in the cytoplasm, is a degradation pathway through which intracellular materials or impaired organelles are transported to lysosomes for clearance (Levy et al., 2017). Autophagy has a dual function in GBM. As a tumor suppressor, it can destroy harmful unfolded proteins, oncogenic protein substrates, and damaged organelles (Batara et al., 2021). For instance, according to recent studies, breast cancer patients with brain metastases may benefit from therapeutic strategies aimed at targeting autophagy (Maiti and Hait, 2021).It may also have a role in protecting GBM cells by eliminating misfolded proteins generated during oxidative stress (Di Rita et al., 2018). Combining standard cancer treatment with the regulation of autophagy activity, by promoting or preventing autophagy using inducers or inhibitors based on tumorigenesis and cancer stages, has the potential to be a promising anti-cancer therapy (Li et al., 2020). Mitophagy refers to the selective removal of damaged mitochondria through the autophagy mechanism to maintain mitochondrial quality and rescue cells from death (Bravo-San et al., 2017; Wang et al., 2018).

These pathways can be classified into typical and atypical. The typical pathway mainly includes PINK1/parkin-, BNIP3/NIX-, and FUNDC1-mediated mitophagy, whereas the atypical pathway mainly includes lipid-, AMBRA1-, BCL2L13-, FKBP8-, and RAB-mediated mitophagy (Vara-Perez et al., 2019). Of note, the autophagy/lysosomal pathway that removes damaged mitochondria (i.e., mitophagy) is impaired in patients with Alzheimer's disease, which leads to the accumulation of dysfunctional mitochondria, leading to synaptic dysfunction and cognitive deficits (Kerr et al., 2017). Dopaminergic neurons selectively fail to execute mitophagy, which promotes their survival(Bernardini et al., 2017; Katayama et al., 2020) within lesions in a mouse model of Parkinson's disease. Rapamycin reduces cisplatin-mediated nephrotoxicity by stimulating PINK1/parkin-mediated mitophagy in renal tubular cells, reducing tissue damage caused by chemotherapy (Wang et al., 2018). Accordingly, mitophagy plays a crucial role in maintaining cellular homeostasis and is a major pathway for the degradation of dysfunctional or damaged mitochondria. Moreover, mitophagy is also a programmed event involved in developmental and differentiation processes, including the elimination of paternal mitochondria from fertilized eggs (Song et al., 2021), as well as the removal of mitochondria during erythropoiesis and muscle differentiation (Senft and Ronai, 2016; Panigrahi et al., 2020) (Figure 1).

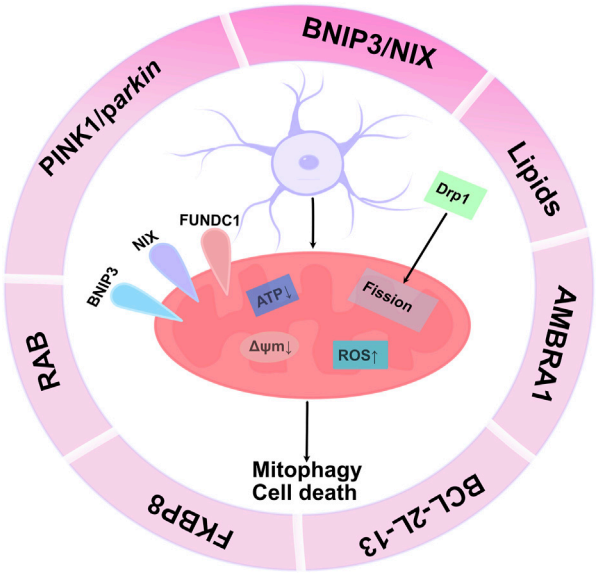

FIGURE 1
Molecular mechanism of mitophagy: The figure reflects mitophagy mediated by receptors (mainly BINP3, NIX, PINK1/parkin, FUNDC1, BCL-2L-13, lipids, RAB, FKBP8). These mitochondrial receptors mediate mitophagy by directly binding to LC3 on autophagosomes via a conserved LIR motif in their N-terminal region. Lipid accumulation on the mitochondrial outer membrane maintains cellular homeostasis, thereby regulating the mitophagy machinery. Hypoxia is an important stimulus that induces this process. PINK1/parkin-mediated mitophagy occurs in a ubiquitination-dependent manner, and ubiquitination of specific mitochondrial proteins enhances phosphorylation of ubiquitin on mitochondrial proteins by PINK1 to recruit mitophagy receptors and mediate the process of mitophagy. After further polyubiquitination, parkin recruits adapter proteins (such as p62/SQSTM1, OPTN) and interacts with LC3 on the membrane surface of autophagosomes to promote mitophagy.

2.2 Relationship between mitophagy and GBM

Activation of mitophagy has been used in the treatment of GBM(Zhou et al., 2020; Wang et al., 2022; Cammarata et al., 2023).It can relieve stress and suppressing tumors by eliminating dysfunctional mitochondria, and mitophagy-mediated clearance of pro-apoptotic mitochondria may provide cytoprotective benefits(Panigrahi et al., 2020). In recent years, studies have shown that drugs related to mitophagy pathways can promote the death of GBM cells by inducing mitochondrial damage, impairing ATP synthesis, and depleting ATP in large quantities. The induction of lethal autophagy has become a strategy to eliminate GBM cells, which is reportedly an effective method to eradicate cancer cells(Maiti et al., 2019; Meng et al., 2022; Rademaker et al., 2022).

2.3 Drugs related to mitophagy

2.3.1 Silibinin

Silibinin is a flavonoid extracted and isolated from the fruit of the chrysanthemum plant Silybum marianum (Tuli et al., 2021). It has been widely used for the treatment and prevention of various hepatobiliary disorders, including alcoholic liver disease, non-alcoholic fatty liver disease, and mushroom poisoning (Abenavoli et al., 2018; Hosseinabadi et al., 2019; Wang et al., 2020a). Recent studies have demonstrated the broad-spectrum anti-cancer effects of silibinin against most types of cancer cells(Jahanafrooz et al., 2018). For example, it can inhibit the migration and invasion of breast cancer MDA-MB-231 cells through induction of mitochondrial fusion(Si et al., 2020). In hepatocellular carcinoma, silibinin has been found to effectively abate hepatocarcinogenesis and hepatocellular carcinoma growth by regulating various signaling pathways including HGF/c-Met, Wnt/β-catenin and PI3K/Akt/mTOR(Yassin et al., 2022). In cholangiocarcinoma, silibinin has the ability to inhibit cholangiocarcinoma through the ERK/mitochondrial apoptotic pathway, which makes silibinin a potential anti-tumor drug candidate for cholangiocarcinoma treatment(Bai et al., 2022).

Considering that silibinin has extremely high antioxidant and anti-tumor properties, it has drawn our attention to its potential use in the treatment of GBM.BNIP3, a member of the Bcl-2 family of pro-apoptotic proteins and a receptor for mitophagy, exhibits context-dependent roles in cancer(Gorbunova et al., 2020; Gorbunova et al., 2020; Vara-Perez et al., 2021).It targets mitochondria and could induce mitochondrial damage and nuclear translocation of AIF6 (Su et al., 2016). A study using GBM cell lines and nude mice with xenografted GBM has confirmed that silibinin could induce mitophagy in GBM, and that autophagy can promote silibinin-induced BNIP3 overexpression and its accumulation in the mitochondria, thereby triggering AIF-dependent death in GBM cells (Wang et al., 2020b). Moreover, silibinin has also been shown to inhibit GBM cell migration by inhibiting MMP-2 and -9 and improving TMZ-resistance in GBM cells (Zhai et al., 2021; Wong et al., 2023). Silibinin have potential uses for patients with GBM. However, like other polyphenols, faces the challenge of low bioavailability, which impedes its potential as a transformative chemotherapeutic drug(Tuli et al., 2021). At the same time, further clinical research is also needed to better understand the potential toxicity and risks associated with the drug's use in treating GBM. This will provide more reliable evidence to support clinical treatment of GBM.

2.3.2 Cannabidiol

Cannabidiol (CBD), the main active component of medical cannabis, is extracted from the wild hemp (Karimi-Haghighi et al., 2022). It easily passes through the BBB, is highly safe, and has anti-proliferation and anti-invasion activities against various cancers (Valenti et al., 2022; Ammendolia et al., 2023). The literature indicates that in many animal cancer models, CBD has shown potential in inhibiting the progression of various types of cancers, including in GBM, breast(Kiskova et al., 2019; Valenti et al., 2022), lung(Milian et al., 2022; Misri et al., 2022), prostate(Mahmoud et al., 2023), colon cancer(Jeong et al., 2019; Lee et al., 2022b; Yuksel et al., 2023), and melanoma(Bachari et al., 2020). CBD has emerged as a promising agent in the treatment of glioma cells due to its ability to inhibit their proliferation and promote cell death. This effect is mainly achieved by targeting the mitophagy pathway, which has gained significant attention in recent research.

Transient receptor potential vanilloid 4 (TRPV4) is a widely expressed multimodal-gated ion channel that plays a pivotal role in many physiological and pathophysiological processes (Grace et al., 2017; Muller and Reggio, 2020). Its expression in human brain basement membrane tissue is closely related to tumor grade and prognosis (Yang et al., 2020). CBD can induce mitophagy by activating endoplasmic reticulum stress via the TRPV4–ATF4–DDIT3–TRIB3–AKT–MTOR axis. TRPV4 expression in human GBM tissues correlates with both tumor grade and poor survival, suggesting that TRPV4 could be an attractive therapeutic target and biomarker for GBM (Huang et al., 2021a). CBD can also lead to abnormal stability of the plasma membrane by affecting the homeostasis of GBM lipid metabolism, thereby promoting the phagocytosis of tumor cells by macrophages and exerting an anti-GBM effect (Khodadadi et al., 2021; Genovese et al., 2022). These two mechanisms synergistically inhibit the formation and development of GBM, indicating that CBD has great clinical application prospects as an anti-GBM medicine et al., 2021).

Simultaneously, compared with single drug treatment alone, the combined treatment of CBD and TMZ more effectively targeted GBM patients, significantly inhibiting the growth of GBM cells and prolonging survival time, suggesting that CBD can effectively enhance the anti-tumor effect of TMZ in GBM (Lopez-Valero et al., 2018; Huang et al., 2021b). Furthermore, in the first study on the CBD-induced anti-tumor effects of RELA Ser311 phosphorylation, ROS was shown to serve as a biomarker for stratifying patients who may benefit from CBD treatment (Volmar et al., 2021).

2.3.3 Gossypol (AT-101)

Gossypol (2,2′-bis-(formyl-1,6,7-trihydroxy-5-isopropyl-3-methylnaphthalene), a BH3-mimetic compound naturally present in cottonseed, exerts anti-tumor effects by targeting various signal transduction pathways. It has been extensively studied in clinical trials, where it has shown good tolerability and safety (Benvenuto et al., 2018; Yurekli et al., 2018). However, recent studies have found that it is the (-)-enantiomer of gossypol, namely (-)-gossypol (also known as AT-101), rather than (+)-gossypol or racemic gossypol, that has significant anti-cancer properties (Benvenuto et al., 2018). Therefore, the development of single-isomer pharmaceutical preparations can avoid potential adverse reactions. Thus far, AT-101 has been considered a promising anti-cancer drug for the treatment of various tumors, including multiple myeloma (Ailawadhi et al., 2023), adrenal cortical carcinoma (Yurekli et al., 2018), esophagus cancer (Que et al., 2019), breast cancer (Bulut et al., 2020), lung cancer (Ahmad et al., 2021; Renner et al., 2022), and prostate cancer (Aktepe and Yukselten, 2022).

HMOX1 is an inducible enzyme that catalyzes the degradation of oxidized preheme and is also involved in mitochondrial biogenesis and mitophagy (Constantin et al., 2012; Hull et al., 2016). AT-101 can promote GBM cell death by inducing overactivation of HMOX1 and the autophagy receptors BNIP3 and BNIP3L, causing early mitochondrial dysfunction and marked loss of mitochondrial mass/protein (Meyer et al., 2018). It also suppresses the growth of TMZ-resistant glioblastoma (Kim et al., 2019). Mitochondrial respiration and mitochondrial permeability transition pore opening were impaired after AT-101 treatment, suggesting that mitochondrial dysfunction is a key driver of AT-101-induced cell demise (Meyer et al., 2018). Because the AT-101 molecule is hydrophobic, oral administration greatly reduces its bioavailability, and gastrointestinal side effects can easily be caused. Therefore, the cyclic RGD (cRGD)-decorated mixed liposome (cRGD-LP) nanopreparation for the tumor-targeted delivery of AT-101 (abbreviated as Gos hereafter) came into being (Xie et al., 2019a; Liu et al., 2022). This nanoformulation enhanced tumor engraftment *in vivo*, possibly due to cRGD binding to the αvβ3 integrin on tumors and tumor cells, enhancing tumor targeting (Liu et al., 2022). Moreover, some studies have also shown that arsenic trioxide-mediated hedgehog/notch inhibition can interfere with DNA double-stranded break repair by reducing the expression of CHEK1 and CHEK2, synergistically targeting GSC along with AT-101 (Linder et al., 2019). AT-101 combined with demethoxycurcumin can enhance the inhibitory effect on the proliferation of glioblastoma cells (Mehner et al., 2020), suggesting that combination therapy with different agents may be an option to overcome drug resistance in GBM cells effectively, in a long-term treatment strategy.

3 Mitochondrial apoptosis and GBM

3.1 Mitochondrial apoptosis

Mitochondria serve as vital organelles in diverse cellular functions, including oxidative phosphorylation, ROS, and calcium signaling, as well as intermediate metabolite synthesis required for cell growth and motility(Bhargava and Schnellmann, 2017). ROS are a crucial class of molecules directly involved in the regulation of mitochondrial function, mainly produced by mitochondrial oxidative phosphorylation. Various cellular metabolic processes are associated with ROS, including transcription factor activation, gene expression, and cell differentiation and proliferation (Thannickal and Fanburg, 2000). Apoptosis is a type of programmed cell death that maintains the homeostasis of the internal environment, which is mainly regulated by the activation of the caspase cascade (Zimmermann et al., 2001). Caspase-3 is considered as the most important regulator of apoptosis, while caspase-9 is considered to be the master regulator of mitochondria-mediated apoptosis (Batoon et al., 2023; Cao et al., 2023). Apoptosis is controlled by intrinsic (mitochondrial pathway) and extrinsic pathways, and the intrinsic pathway is regulated by the BCL-2 family, including the anti-apoptotic activator BCL-xL and proapoptotic effector BAX(Lindenboim et al., 2000). Cell stress induces the proapoptotic effector BAX to induce cell apoptosis by inducing the release of cytochrome-c (Cyt-C), a key component of the mitochondrial electron transport chain, into the cytoplasm (Finucane et al., 1999; Desagher and Martinou, 2000). In the extrinsic pathway, caspase-8 cleaves and activates procaspase-3 (Boatright and Salvesen, 2003). However, the result of both pathways is caspase activation and the cleavage of specific cellular substrates, leading to morphological and biochemical changes associated with an apoptotic phenotype (Lee et al., 2020). In this process, apoptosis is characterized by the formation of apoptotic bodies, containing the contents of dead cells, which will be engulfed by the surrounding cells without

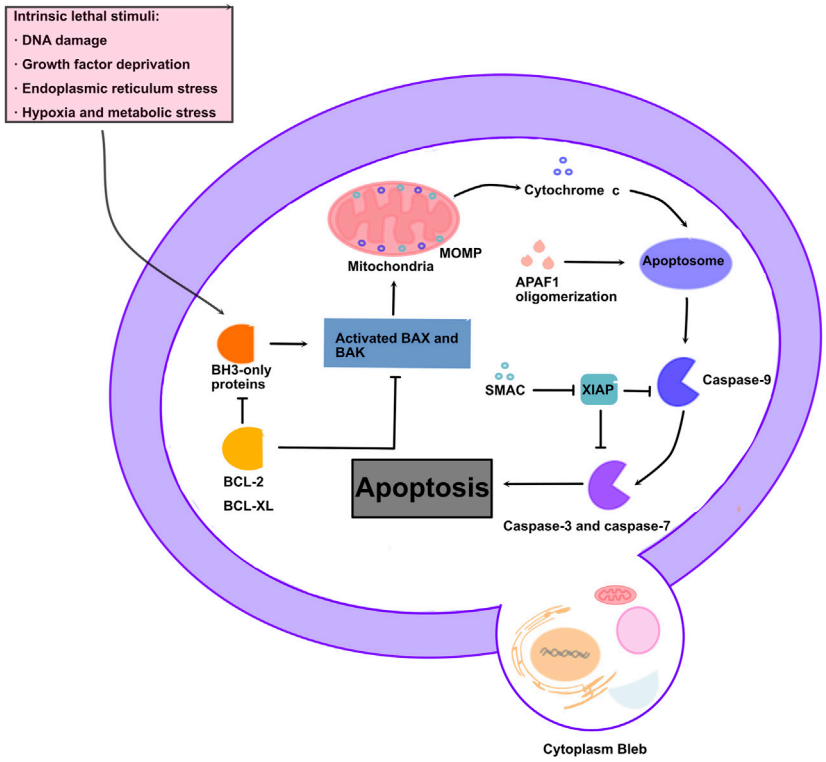

FIGURE 2
Molecular mechanism of mitochondrial apoptosis: Apoptotic stresses promote accumulation of BH3-only proteins leading to BAX/BAK oligomerization, MOMP, and release of intermembrane space proteins. Cytochrome c leads to apoptosome formation, which results in caspase activation and apoptosis.

causing content leakage or damage to the surrounding cells (Li et al., 2021) (Figure 2).

3.2 Relationship between mitochondrial apoptosis and GBM

The accumulation of intracellular ROS can cause carcinogenesis. In GBM cells that require high levels of ROS, if ROS are lower than the minimum level for GBM cell survival, it may induce intracellular signaling disturbances and apoptosis (Huang et al., 2021a; Huangfu et al., 2021). The accumulation of mutations in mitochondrial DNA (mtDNA) contributes to mitochondrial dysfunction, which plays a crucial role in the pathogenesis of GBM. This dysfunction leads to abnormal energy and reactive oxygen species production, as well as resistance to apoptosis and chemotherapeutic agents(Leao et al., 2021).While many chemotherapeutic drugs play a tumor-killing role by inducing ROS and enhancing oxidative stress, they can also damage the mitochondria and DNA of normal cells and even induce carcinogenesis in other cells (Kleih et al., 2019). Therefore, regulating the level of ROS in tumor and normal tissues and selectively killing tumor cells has great clinical significance (Di Meo et al., 2022). Mitochondria are considered to be novel targets for cancer intervention and therapy (Xu et al., 2009). It can induce apoptosis in GBM cells by disrupting the balance in the anti-oxidant system, which are important mechanisms in the research of anti-tumor therapies (Benlloch et al., 2016; Feng et al., 2016).

3.3 Drugs related to mitochondrial apoptosis

3.3.1 Xanthohumol

Xanthohumol (XN), a natural compound found in hops, is an isoprene flavonoid with a wide range of biological activities, including anti-inflammatory, anti-oxidant, anti-cancer, antibacterial, and lipid lowering (Lin et al., 2022c; Neumann et al., 2022). Since flavonoids readily cross the BBB *in vivo*, they are considered potential drug leads for treating disease. Several studies have shown that XN has anti-GBM effects. It can not only inhibit the IGFBP2/AKT/BCL-2 pathway and activate the P53 signaling pathway to participate in XN-induced GBM cell apoptosis (Chen et al., 2016), but it also induces apoptosis of glial pathway cells by increasing ROS and activating MAPK pathways (Festa et al., 2011). Hou et al. confirmed that XN can inhibit C6 proliferation, trigger mitochondrial stress, and induce cell death in a concentration- and time-dependent manner (Hou et al., 2021). Following treatment of GBM cells with XN, the cell cycle was blocked at the G0/G1 phase, and XN induced AIF-mediated apoptosis, which was accompanied by mitochondrial structure and function impairment, as well as mitophagy blockage (Hou et al., 2021). In contrast, mitochondrial injury not only disrupts

ATP synthesis in cells but also consumed large amounts of ATP to maintain intracellular stability. This vicious cycle exacerbates cellular energy consumption. The DNA repair machinery is a tool to remove DNA damage for the maintenance of genomic integrity in normal cells and paradoxically plays a crucial role in driving the development of drug resistance and tumor recurrence (Huang and Zhou, 2021). The results of Ho et al. showed that XN could enhance the cytotoxicity of TMZ by inhibiting the DNA repair system and could be used as an adjuvant drug in the treatment of patients with GBM with DNA repair activation (Ho et al., 2020). Moreover, XN also reduces the invasiveness of GBM cells by inhibiting the signaling of stromal interacting molecule 1 (STIM1), indicating that XN may be a good GBM therapeutic agent (Ho et al., 2018). Elucidating the XN-mediated molecular mechanism may provide novel strategies for future drug development and tumor research.

3.3.2 Pterostilbene

As a methylated derivative of resveratrol, pterostilbene (PTE) has higher biological activity and safety than resveratrol and is mainly found in blueberries and grapes (Rimando et al., 2004; Ruiz et al., 2009; Chang et al., 2012). PTE has a wide range of biological functions, including anti-tumor, anti-oxidation, anti-inflammatory, apoptosis, cardiovascular protection, anti-proliferation, and antibacterial activities (Chen et al., 2020), gallbladder (Tong et al., 2021), breast (Harandi-Zadeh et al., 2021; Kumar et al., 2021), colon (Wawszczyk et al., 2022), cervical (Shin et al., 2020), prostate (Hemani et al., 2022), and lung cancers (Bracht et al., 2019). In GBM, PTE can induce the loss of mitochondrial membrane potential and production of reactive oxygen species (ROS) (Gao et al., 2021) and activate the FAS/FASL pathway and caspase-3, thereby inhibiting proliferation and inducing GBM cell apoptosis (Tan et al., 2019; Gao et al., 2021). Moreover, given that PTE presents highly bioavailability and easily crosses the BBB, PTE administration can serve as a novel treatment for patients with GBM (Ma et al., 2019). Based on the abovementioned experimental results, PTE has a high research value and development prospects in the field of GBM drug treatment.

3.3.3 Chrysophanol

Chrysophanol (1, 8-dihydroxy-3-methyl-9, 10-anthraquinone) is a phytochemical extracted from Rheum officinale (rhubarb), which has been utilized as a traditional Chinese herbal medicine (Yusuf et al., 2019; Su et al., 2020). It has various pharmacological effects, including anti-cancer, antioxidant, neuroprotective, antibacterial, antiviral, and blood lipid-regulation effects. Studies have shown that chrysophanol can attenuate hepatic stellate cell-induced endoplasmic reticulum fibrosis by regulating hepatitis B virus stress and iron concentration (Kuo et al., 2020). Moreover, it can inhibit the growth and metastasis of T-cell acute lymphoblastic leukemia through the miR-9/PD-L1 axis (Yin et al., 2021), regulating the effect of the microRNA-27b-3p/peroxisome proliferator-activated receptor γ axis on sepsis-induced acute myocardium damage protection (Park et al., 2022).

Moreover, the application of chrysophanol for cancer treatment is also increasing. For instance, chrysophanol promotes cell morphological changes, induces cell apoptosis through DNA damage, and arrests S phase cell cycle among patients with liver cancer (Ni et al., 2012). In patients with lung cancer, chrysophanol expresses anti-cancer activity by regulating the ROS/HIF-1a/VEGF signaling pathway (Zhang et al., 2020a; Zhang et al., 2021a). In patients with GBM, it has been discovered that chrysophanol increased the accumulation of ROS in the mitochondria of GBM cells, promoting the release of Cyt-C from the mitochondria to the cytoplasm and, thereby, causing GBM cell apoptosis (Gu et al., 2021). Chrysophanol regulates the anti-cancer effect on GBM cells by activating the mitochondrial apoptosis pathway, indicating that it may serve as an innovative chemotherapeutic agent for GBM. However, chrysophanol has obvious hepatotoxicity and nephrotoxicity. Nevertheless, pharmacokinetics has shown that chrysophanol combined with other drugs can reduce toxicity and improve efficacy (Xie et al., 2019b).

3.3.4 Shikonin

Shikonin is the main bioactive component extracted from the root of Lithospermum erythrorhizon, which has various bioactivities related to cancer treatment, inflammation, and wound healing. Many studies have shown that shikonin has strong anti-cancer effects on leukemia, gastrointestinal cancer, pancreatic cancer, lung cancer, breast cancer, and urogenital organ cancer, by inhibiting cell proliferation and migration, and inducing apoptosis and necroptosis (Guo et al., 2019). A clinical trial conducted by Guo et al. reported that, among 19 patients suffering from late-stage lung cancer who were not subjected to surgery, chemotherapy, or radiotherapy, the tumor diameter decreased by more than 25% after treatment with shikonin, posing a remission rate of 37% and a 1-year survival rate of 47% (Boulos et al., 2019). Shikonin is a potent inducer of necrotizing apoptosis in cancer cells. In terms of pharmacological mechanism, anti-glioma effect of shikonin by interfering with endoplasmic reticulum stress-mediated tumor apoptosis targeting Caspase-3, and Bax/Bak-induced mitochondrial outer membrane permeabilization (MOMP) triggering cancer cell apoptosis (Ma et al., 2020). ROS is the executor of necrotizing apoptosis. Shikonin increases intracellular ROS levels by targeting both NOX1 and the mitochondrial respiratory chain complex (Yang et al., 2014). RIP1 and RIP3 can modulate shikonin-induced ROS overproduction by targeting the mitochondria and promoting RIP1/RIP3-dependent necroptosis in GBM cells (Lu et al., 2017). Shikonin has shown great promise as a potential drug for treating glioma by targeting the mitochondrial apoptosis pathway. In order to achieve greater precision and efficacy in treating glioma, it is necessary to consider the shikonin's ability to cross the blood-brain barrier. Wang et al. developed an AS1411 aptamer/hyaluronic acid-bifunctionalized microemulsion co-loading shikonin and docetaxel (AS1411/SKN&DTX-M), which has the ability to penetrate the BBB according to their research report. The codelivery of shikonin and docetaxel through bifunctionalization with hyaluronic acid and AS1411 aptamer presents a promising approach for anti-GBM therapy using dual-drug therapy (Wang et al., 2019).

3.3.5 Grape seeds

Grape seeds are the seeds of Vitis vinifera. Grape seed proanthocyanidins (GSP) is a general term for a large class of polyphenolic compounds that have antioxidant activity. GSP has

various biological activities and has been proven to have good anti-tumor effects, as well as certain inhibitory effects on cervical cancer (Li et al., 2022a), carcinoma of the urinary bladder (Yang et al., 2021a), lung cancer (Xu et al., 2021a; Zhang et al., 2021; Mao et al., 2023), colon cancer (Aiello et al., 2019; Zhang et al., 2019), liver cancer (Feng et al., 2019), prostate cancer (Chen and Yu, 2019), among others. In a study on liver cancer cells, GSP was found to trigger ROS production, decrease matrix-metalloproteinases (MMPs), and increase caspase-3 activity in HepG2 cells (Wang et al., 2020), proving that GSPs may induce ROS production and, consequently, lead to MMP reduction and caspase-3 activation. This ultimately induces HepG2 cell apoptosis. GSP can reverse EMT by inhibiting the TGF-β signaling pathway, effectively inhibiting the migration and invasion of bladder cancer (BC) cells (Yang et al., 2021b), suggesting that GSP can be used as a potential chemotherapy drug for BC. GSP can also reduce the proliferation activity of cancer cells (Habib et al., 2022). The mechanism of GSP pertaining to GBM is related to the inhibition of proliferation, induction of apoptosis, arrest of the cell cycle, and inhibition of angiogenesis and metastasis (Yang et al., 2021b). Grape seed, as a natural anti-cancer drug, holds great promise for the treatment of glioma. However, further clinical research is necessary to fully elucidate its role in the treatment mechanism.

3.4 Drugs related to mitochondrial apoptosis and mitophagy

3.4.1 Sinomenine

The alkaloid sinomenine (SIN), namely 7,8-didehydro-4-hydroxy-3,7-dimethoxy-17-methylmorphinan-6-one (C19H23NO4), is extracted from the rhizome of the traditional Chinese medicine plant Sinomenium acutum (Zheng et al., 2021). SIN has anti-inflammatory effects and has been used to treat rheumatoid diseases in humans (Lin et al., 2022b; Chen et al., 2022). In recent years, SIN and its derivatives have been reported to have strong anti-tumor activity against various tumors, including BC (Xu et al., 2021b), prostate (Xu et al., 2019), papillary thyroid (Zhang et al., 2022b), breast (Li et al., 2022b; Gao et al., 2022), ovarian (Qu et al., 2021), and lung cancers (Bai et al., 2021). SIN can inhibit cell proliferation (Sun et al., 2018a; He et al., 2018), induce apoptosis (Liu et al., 2019) and arrest the cell cycle at the G0/G1 phase in various cancers (Yang et al., 2021a). SINI-WCJ-33 (SW33, C33H51NO5), a SIN-derivative obtained by the acylation of 4-hydroxyl and 14-carboxylic acid, can inhibit the proliferation, migration, invasion, and colony formation of human glioblastoma cell lines (Zheng et al., 2021). This derivative has higher anti-GBM activity and safety than its parent compound (Liu et al., 2019). The CCNB1/CDC2 complex is a key mediator of the G2/M checkpoint (Park et al., 2000; Taylor and Stark, 2001; Cheng et al., 2016). The polo-like kinase (PLK1)-dependent phosphorylation of CDC25C is required for normal cell cycle progression from the G2/M phase (Liu et al., 2020b; Tang et al., 2020). SW33 can reduce the expression of P-CDC2, CDC2, and CCNB1, as well as the protein levels of P-PLK1 and PCDC25C in GBM cells. It can also increase the expression of P53 and its transcriptional target P21, finally leading to the arrest of the GBM cell cycle in the G2/M phase, causing mitochondrial dysfunction, consequently releasing Cyt-C, activating caspase 3/9, and inducing mitochondrial apoptosis (Zheng et al., 2021).

In addition, PI3K/AKT/MTOR, MAPK/MTOR, and AMPK/MTOR have been widely reported to activate mitophagy (Zhang et al., 2020b; Liu et al., 2021). Zheng et al. have shown that SW33 can induce autophagy through the PI3K/AKT/MTOR and AMPK/MTOR signaling pathways in patients with GBM, thus playing an anti-GBM role, significantly inhibiting tumorigenesis, without having obvious adverse effects on the body (Zheng et al., 2021). Taken together, all these results suggest that SW33 may be a promising drug for the treatment of GBM.

4 New advances in drug therapy for GBM

4.1 The application of nanotechnology in GBM

The BBB comprises multiple components with barrier functions, including polarized endothelial cells connected by continuous adhesive and tight junctions, endothelial and parenchymal basement membranes, pericytes, and astrocyte foot processes (endfeet) (Steeg, 2021). As a barrier between circulating blood and brain parenchyma, it can prevent blood-borne pathogens or toxic substances from entering the CNS, maintain the dynamic balance of the CNS, and prevent the effective passage of cancer treatment drugs, including antibodies and miRNAs (Sarkaria et al., 2018). The concept of the BBB was first proposed by Edwin Goldman in 1913, who observed the limited transport of dye between the blood and brain. After injecting dye into the veins and CSF of animals, dye was distributed in almost all organs, except the brain (Langen et al., 2019). The disruption of the BBB during tumor progression results in the formation of the blood-tumor barrier (BTB) (Steeg, 2021). While the BTB is more permeable than the BBB, its uneven permeability to molecules of different sizes and uneven blood flow can lead to less than ideal drug accumulation in brain tumors(Arvanitis et al., 2020; Steeg, 2021).With significant advances in nanotechnology, various inorganic/organic/natural nanomaterials that target ligands and/or cell-penetrating peptide (CPP) surface modifications through the BBB have been created to help drugs cross the BBB to induce mitochondrial dysfunction for highly precise therapy (Tang et al., 2019).

4.1.1 Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) (RES) is a naturally occurring polyphenol and phytoalexin that is abundant in red wine, berries, peanuts, and soybeans and has anti-inflammatory, anti-oxidant, anti-cancer, cardioprotective, and neuroprotective effects (Baur and Sinclair, 2006; Catalgol et al., 2012; Neves et al., 2012). Resveratrol is effective in the treatment of GBM through various mechanisms, but its bioavailability is severely reduced due to its poor water solubility, short biological half-life (approximately 9–14 min for primary molecules), chemical instability (oxidation and photosensitivity), and rapid metabolism and elimination (Jhaveri et al., 2018). If its shortcomings as a free drug can be overcome, its *in vitro* activity could be enhanced, and the relevant

therapeutic effect could be improved. Triphenylphosphine (TPP+) is a lipophilic cation that can couple many bioactive molecules to achieve mitochondrial targeting (Wang et al., 2021). According to a report, paclitaxel-loaded liposomes prepared using TPP- modified polyethylene glycol-phosphatidylethanolamine (PEGPE) have been shown to be effective in targeting mitochondria in cancer cells (Biswas et al., 2012). Loading RES into PEGylated liposomes (RES-Ls) has been reported to overcome its drawbacks as a free drug (Fu et al., 2021). Furthermore, transferrin is overexpressed on most cancer cells, and transferrin-targeted RES-Ls may be an effective nanomedicine for the treatment of various cancers, including GBM, even though their biodistribution *in vivo* and ability to cross the BBB remain unknown.

4.1.2 Berberine

Berberine (BBR) is a natural compound isolated from Chinese herbal medicine, including the Coptis root (Huang Lian) and Amur corktree (Huang Bai). It has a wide range of pharmacological effects, including antidiarrheal, antibacterial, antioxidant, anti-inflammatory, and anti-tumor aspects (Li-Weber, 2013; Li et al., 2015). BBR can inhibit GBM cell growth, reduce cellular viability, and induce oncosis-like death (cell swelling, cytoplasmic vacuoles, and plasma membrane blebbing) (Sun et al., 2018b). We also found that BBR induces autophagy as a protective effect and decreases the oxygen consumption rate, which could inhibit mitochondrial aerobic respiration by repressing phosphorylated extracellular regulated protein kinases (p-ERK1/2), reducing its energy production efficiency and, thereby, reducing metabolic activity (Sun et al., 2018b). The most challenging aspect related to BBR or other therapeutics in GBM is crossing the BBB. Glucose-coated nanodrugs and fructose-coated nanoparticles can provide 10–100-times more uptake by tumor cells in various models (Hu et al., 2015). The formation of nanoshapes by simply dissolving BBR into 5% glucose solution provides a promising strategy for drugs to cross the BBB (Wang et al., 2020).

4.2 Sonodynamic therapy

Sonodynamic therapy (SDT) is a technique that involves using focused ultrasound (FUS) to increase the sensitivity of tumors to sonosensitizers during sonication (Mess et al., 2023).It has shown promise as a cancer therapeutic modality for GBM due to its high tissue penetration and minimal radiation damage to normal tissues (Zhang et al., 2021c). Despite the potential of SDT in eliminating tumor cells, its effectiveness is limited by the BBB and the low accumulation rate of sonosensitizers (Guo et al., 2022). As a result, complete eradication of tumor cells cannot be guaranteed through SDT.Therefore, to improve the efficiency of drug delivery and further reduce adverse reactions, ultrasound-targeted microbubble destruction has been developed. It is a non-invasive technology that combines low-intensity FUS and microbubbles (MBs), which can transiently and reversibly destroy the BBB and promote drug delivery in the brain with a high degree of spatial and temporal specificity (Gorick et al., 2018). Low-intensity FUS has been explored as a drug delivery platform for the treatment of brain diseases (Landhuis, 2017), which can promote the deep penetration of SDT and the accumulation of tumor-specific sonosensitizing agents (Yeshurun and Azhari, 2016). SDT often concomitantly initiates an autophagic response during tumor cell apoptosis induction (Zhao et al., 2011). Excessive ROS production by ACL-SDT induces mitochondrial dysfunction and leads to MAPK/p38-PINK1-PRKN-dependent mitophagy (Qu et al., 2020). Mitophagy plays a protective role under oxidative stress, and inhibition of the degradation pathway significantly enhances the SDT-induced apoptosis of GBM cells (Qu et al., 2020). The lysosomal chemoattractor hydroxychloroquine (HCQ) is the only clinically available autophagy inhibitor (Cook et al., 2014). Qu et al. designed an "all-in-one" nanosensitization platform incorporating Ce6 and HCQ into angiopeptide-2 peptide-modified liposomes and designated a smart nanosensitizer, that can be used to treat GBMs *in situ* (Qu et al., 2020). Combining autophagy inhibitors with non-invasive SDT therapy provides a promising anti-GBM strategy, and the "all-in-one" nanosensitization platform is expected to be extended to other sonotheranostics in future.Besides, the efficiency of SDT can be enhanced by using a nano-platform biodegradation technology called CSI. This involves encapsulating catalase (CAT) into silica nanoparticles (CAT@SiO2) to alleviate tumor hypoxia, and then loading it with the sonosensitizer indocyanine green, which significantly improves the efficacy of SDT(Wu et al., 2022). The combination of SDT and natural drugs targeted to mitochondria can significantly enhance the therapeutic efficacy against glioma, which holds great importance for precise treatment of this disease.

5 Summary

GBM is the most common primary malignant brain tumor with high metabolic activity. Currently, GBM is treated by removing the tumor to the maximum extent and combining it with chemotherapy (Molinaro et al., 2022). However, due to its invasiveness, the total resection rate is low, the residual tumor tissue has obvious resistance to radiotherapy and chemotherapy, and the long-term survival rate of patients with GBM is low (Yi et al., 2019). The presence of the BBB further complicates the treatment process. Despite significant progress in the standard of care for GBM, including surgery, radiation therapy, and medical therapy such as chemotherapy with TMZ, patient outcomes remain extremely poor with a low median overall survival rate. GBM is still considered a fatal disease with limited treatment options.Given the extremely low survival rates of currently approved treatments for GBM, new therapeutic strategies are urgently needed. The clinical reality of the BBB contribution to GBM treatment failure suggests that renewed efforts to optimize BBB disruption techniques, develop BBB penetrators, and perfect impenetrable drug delivery technologies that bypass the BBB are the focus of current GBM treatment research. With the development of comprehensive treatment for glioblastoma in recent years, the anti-cancer effects of natural products and phytochemicals commonly used in traditional Chinese medicine continue to attract widespread attention. But the BBB presents a challenge for the effective delivery of anticancer drugs to the brain, limiting their curative effects.Modern nano-drug delivery technology targeting mitochondria can achieve better drug release and deeper tissue penetration, suggesting that mitochondria could be a new target for intervention and therapy. The combination of drug targeting mitochondrial apoptosis and autophagy pathways with

nanotechnology is a promising novel approach for treating GBM. However, it is a particularly challenging task to engineer nanoformulations that can perfectly target mitochondrial abnormalities in tumor cells without causing toxic effects on nearby normal cells. Since most of our experiments were carried out on animal models, further research is needed to explore the safety parameters of ultrasound in GBM.With the rapid advances in knowledge and nanomedicine for GBM, increasing numbers of molecular targets have been identified, providing a solid foundation for the development of precise nanotherapeutic systems in future.We look forward to the development of more effective drugs for GBM treatment, focused on the mitochondrial pathway, and the emergence of more mature nanoagents combined with nanotechnology to kill tumor cells specifically, improving the therapeutic effects of medicine for GBM.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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