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Review Article

The role of PI3K/AKT signaling pathway in gallbladder carcinoma

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Abstract: Objectives: The prognosis of gallbladder carcinoma (GBC) is poor, with a less than 5% five-year survival rate. Identifying the mechanisms underlying GBC occurrence and advancement is necessary to improve GBC patient prognosis and survival rates. The phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (AKT) pathway is involved in cancer deterioration, tumor growth, cell proliferation, and distant metastasis. Studying the impacts of the PI3K/AKT pathway has resulted in the identification of key factors involved in GBC progression that might serve as therapeutic targets, promoting the development of new treatments. Methods: We reviewed recent literature exploring abnormal regulation of the PI3K/AKT pathway in gallbladder cancer, with a focus on abnormal RNA levels, protein level regulation, and drug treatment advances. Results: Further investigation of the regulation of small molecules and proteins by the PI3K/AKT pathway might ultimately provide new diagnostic or prognostic markers or cancer treatment targets. Recent studies have focused on RNA and proteins involved in the regulation of the cell cycle or cell movement in cancer progression via PI3K/AKT pathway, the use of anticancer drug combinations, or the anticancer effects of drugs not currently utilized for cancer treatment. Conclusions: We herein review the known available molecules that affect the PI3K/AKT pathway in patients with GBC and the mechanisms of drug action associated with this pathway.

Keywords: PI3K/AKT pathway, gallbladder cancer, crosstalk, regulation, mechanism, protein, chemotherapeutic agent

Introduction

The overwhelming majority of biliary tract malignancies are gallbladder carcinomas (GBCs), accounting for approximately two-thirds of total cases [1]. GBC has a low survival rate of 17.8%-21.7%, with a median survival of 6 months. Gallbladder cancer is relatively rare, but it is still the sixth most common gastrointestinal cancer worldwide [2]. GBC is an intractable malignancy and is designated as an orphan disease [3, 4]. Although GBC morbidity is lower compared to other gastrointestinal cancers, the survival rate is low due to the reduced chance of early diagnosis with rare specific symptoms in the early stage, so that more than 90% of patients are diagnosed at the advanced stage [5, 6]. The 5-year survival rate of T1 GBC patients is 95%-100%, but the rate for patients with T3 stage and T4 stage is only 23% and 12%, respectively. Early metastasis can occur, and the degree of malignancy is high, with a five-year survival rate of less than 5% [7, 8]. Although surgery is the primary curative treatment, access to surgery is limited to fewer than 10% of patients because most gallbladder cancer patients present with local metastases or are diagnosed at advanced stages [9-11]. Identifying specific molecular changes in different patients and the utilization of appropriate targeted therapies is changing current therapies and treatment paradigms [12, 13]. Even so, the prognosis for patients receiving combination chemotherapy remains poor, with an

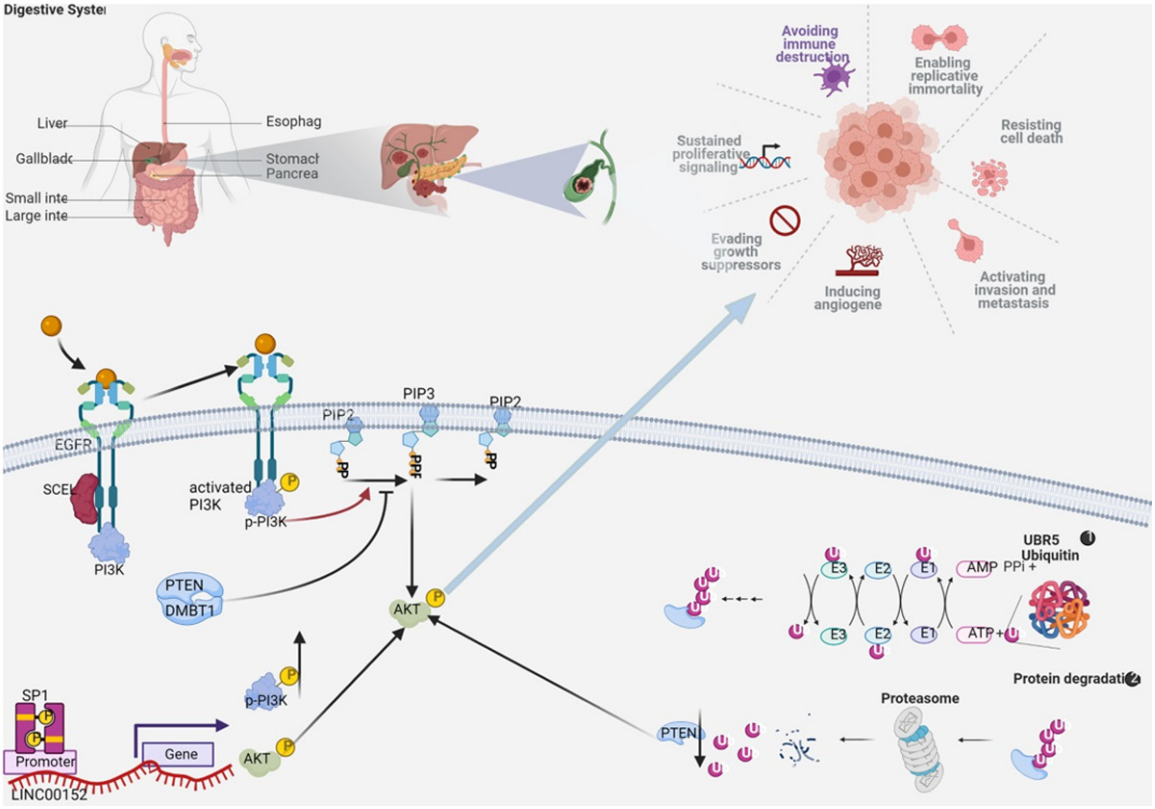

Figure 1. Many RNAs, proteins, and drugs can directly or indirectly interact with the PI3K/AKT pathway, exerting their respective carcinogenic or anticancer effects. PTEN is a tumor suppressor and its inactivation can lead to carcinogenesis. UBR5, which is a key regulator of the ubiquitin-proteasome system, can inactivate PTEN by ubiquitination. In contrast, DMBT1 can directly bind with and stabilize PTEN to reverse the phosphorylation of AKT. Furthermore, *LINC00152* can function as a cancer promotor by directly producing p-AKT and p-PI3K without changing the number of PI3K and AKT.

average life expectancy shorter than 1 year. The main obstacles to treating gallbladder cancer are the lack of biomarkers for early diagnosis and molecular targets for targeted therapies [7, 14]. Therefore, it is imperative to more fully understand GBC molecular pathogenesis to develop more effective treatment options for GBC patients.

Phosphatidylinositol-3 kinase (PI3K) phosphorylates the 3'-OH group on the inositol ring to generate the second messenger phosphatidylinositol-3, 4, 5-trisphosphate (PIP3). PI3K is an intracellular lipid kinase involved in the regulation of cellular processes, such as proliferation, differentiation, and apoptosis [15]. Protein kinase B (AKT) is a proto-oncogene product that regulates various cellular processes, including proliferation, growth, apoptosis, transcription, and protein synthesis. PI3K is an important component that activates the AKT signaling cascade, triggering the production of PIP3 [16]. AKT is recruited and activated by binding to PIP3 and subsequently regulates cellular processes, ultimately playing an important role in tumorigenesis and tumor progression [17, 18]. The PI3K/AKT pathway, which plays key roles in cell proliferation, angiogenesis, multidrug resistance, invasiveness, and metastasis, consists of the upstream membrane receptor PI3K, the second signaling protein PIP3, AKT, and the downstream membrane [19-21]. Cancer-related abnormalities in PI3K/AKT pathway components lead to the dysregulation of PI3K/AKT signaling and downstream effectors, causing diverse problems that can hamper cancer treatment. Multiple studies suggest that the PI3K/AKT pathway is upregulated in GBC.

This review aims to explore the latest progress toward understanding the relevant molecular mechanisms and key molecules involved in PI3K/AKT signaling pathway regulation that could provide greater insight into improving existing treatments for GBC (**Figure 1**).

PI3K/AKT pathway and post-transcriptional control

In the past few years, the roles of non-coding RNA and gene mutations have attracted increasing attention in human cancers [22-24]. Therefore, it is necessary to focus on these novel targets and explore their relationships (**Table 1**).

Long intergenic non-coding RNA 152 (*LINC-00152*) has been reported to be tumor-promotive in diverse cancers, including colorectal cancer [25], lung cancer [26], and hepatocellular carcinoma [27]. *LINC00152* is upregulated in GBC tissues and cell lines. Additionally, its level is related to clinical characteristics, including tumor status, lymph node status, and stage. Furthermore, *LINC00152* is associated with cell proliferation, apoptosis, and metastasis *in vitro*. The above effects are mediated by SP1, a transcription factor that can directly drive *LINC00152* expression by binding to the *LINC00152* promoter in GBC cells. The upregulation of *LINC00152* by SP1 activation in GBC is induced by the activation of the PI3K/AKT pathway [28]. Therefore, SP1, *LINC00152*, and the PI3K/AKT signaling pathway all have the potential to serve as prognostic markers or therapeutic targets in novel GBC management strategies.

Studies have revealed that miR-143-3p could function as a tumor suppressor that inhibits GBC cell proliferation and angiogenesis *in vivo* and *in vitro* [29-32]. Integrin subunit alpha 6 (ITGA6) is a direct downstream target of miR-143-3p that exhibits high expression levels in GBC, and ITGA6 expression is negatively associated with miR-143-3p expression in GBC [33]. Reports show that miR-143-3p/ITGA6 functions as a key mediator of angiogenesis regulation via the PI3K/AKT/signal transducer and activator of the transcription 3 (STAT3) pathway. Placental growth factor (PIGF), which is part of the vascular endothelial growth factor family, can directly promote vessel extension by stimulating endothelial and mural cells. Additionally, PIGF overexpression has been reported to promote tumor growth and angiogenesis [34, 35]. Findings show that miR-143-3p downregulates PIGF expression via the ITGA6/PI3K/AKT pathway in GBC, further supporting a role for miR-143-3p in GBC prevention [33]. The use of miR-143-3p could be a unique solution to overcome the highly invasive force of gallbladder cancer.

Factors with more complex structures are more likely to present with abnormalities. Abnormal gene expression is essential for tumorigenesis. The *PIK3CA* E545K mutation was first reported in 2005 and has been identified in melanoma, cervical cancer, breast cancer, and GBC [36-38]. Additionally, the E545K mutation has been significantly associated with overall survival in patients with GBC [39]. Further research showed that the *PIK3CA* E545K mutation is crucial for the proliferation, distant migration, organ invasion, and clonal formation of GBC cells *in vitro* and *in vivo* by increasing downstream AKT activation [40]. *PIK3CA* encodes the alpha catalytic subunit of PI3K, and the E545K mutation might enhance PI3K binding to epidermal growth factor receptor [41]. Studies have also shown that a selective PI3K p110α inhibitor can suppress GBC progression [40]. Overall, these findings may lead to the development of a new therapeutic strategy that targets the E545K mutation.

One of the most sophisticated eukaryotic translation initiation factors is eukaryotic initiation factor 3 (eIF3). The eIF3 subunits are altered in human cancers, which may account for the observed abnormal oncogene expression levels and neoplastic transformation [42]. eIF3d, a core subunit of eIF3, is reported to play an important role in GBC carcinogenesis by enhancing the stability of G protein-coupled receptor kinase 2 (GRK2) and activating the PI3K/AKT pathway [43]. The C-terminal region of eIF3d can directly interact with and stabilize GRK2 by preventing the ubiquitin-mediated proteasomal degradation of GRK2. GRK2 has been reported to activate various pathways involved in the occurrence and deterioration of cancer [44-46], such as malignant cell proliferation, cell motility, and metabolism, and GRK2 has been reported to activate the PI3K/AKT pathway, which is a critical downstream event in diverse cellular activities associated with GBC [47]. Therefore, targeting eIF3d and GRK2 may offer efficient treatment options for GBC patients [47].

PI3K/AKT pathway and translation products

Protein is the material basis of life, the organic substance forming the basis of cells, and the principal undertaker of cellular activities. In addition to being the product of gene expression, proteins can act on genes themselves, altering cellular processes by regulating related pathways (**Table 2**).

Table 1. The expression levels of several RNAs and occurrence of genetic mutation are associated with clinical features and cellular activities of GBC patients

Related Gene	Expression in GBC	Clinical feature	*In vitro*	*In vivo*	Property	Related genes	Reference
miR-143-3p	Downregulation	Tumor size and invasion	cell proliferation and angiogenesis	angiogenesis and tumor growth	Antioncogene	miR-143-3p, ITGA6, PI3K, AKT, STAT3	[33]
LINC00152	Upregulation	Tumor status, lymph node status and clinical stage	cell proliferation and metastasis; apoptosis	tumorigenicity	Oncogene	LINC00152, PI3K, AKT	[28]
EIF3D	Upregulation	Overall survival	proliferation, cell cycle, and migration	xenograft tumor formation and growth	Oncogene	EIF3d, GRK2, PI3K, AKT	[47]
E545K mutation of PIK3CA	Upregulation	Advanced clinical stage lymph node metastasis; overall survival	proliferation, migration, invasion and clone formation	tumor volumes and weights	Oncogene	E545K mutation of PIK3CA, AKT	[40]

Table 2. The crosstalk of following proteins and PI3K/AKT pathway induces or promotes the occurrence and development of GBC to varying degrees

Protein	Expression	Clinical feature	In vitro	In vivo	Property	Function to PI3K/AKT Pathway	Reference
INPP4B	Overexpression	overall survival	proliferation, cell migration and invasion; apoptosis rate	/	promoter	promote	[96]
BRD4	Overexpression	pathologic T stage, lymph node metastasis and TNM stage; overall survival time	cell proliferation and colony formation capacity; metastatic capacity and apoptosis	tumor growth	promoter	promote	[78]
LASP-1	Overexpression	survival rate; lymph node metastasis	metastatic capacity, migration and invasion; arrest G2/M phase	tumor volume	promoter	promote	[75]
SP1	Overexpression	tumor status progression lymph node invasion, TNM stage advancement	proliferation, cell migration and invasion and cell apoptosis	tumor growth	promoter	activate the PI3K/AKT pathway	[28]
TASP1	Overexpression	/	cell proliferation; migration and invasion	tumor volume and weight	promoter	activate PI3K/AKT pathway	[77]
TRIM31	Overexpression	histological grade, lymph node metastasis, and TNM stage	proliferation, migration and invasion	tumor growth and metastasis	promoter	activate PI3K/AKT pathway	[90]
UBR5	Overexpression	tumor size, histological tumor differentiation	proliferative capacity	tumor size	promoter	PTEN/PI3K/AKT pathway	[51]
KIF11	Overexpression	/	cell proliferation, accelerate G2/M cell cycle	tumor growth	promoter	ERBB2/PI3K/AKT pathway	[56]
SPOCK1	Overexpression	histological differentiation, lymph node metastasis, and overall survival	cell proliferation, migration and invasion; apoptosis	migration and invasion	promoter	activate PI3K/AKT pathway	[64]
STYK1	Overexpression	tumor size, lymph node metastasis, and overall survival	proliferation, migration and invasion; cell apoptosis	tumor growth	promoter	activate PI3K/AKT pathway	[66]
DMBT1	Downregulation	/	apoptosis	GBC growth	Suppressor	suppress PI3K/AKT pathway	[59]

Ubiquitin protein ligase E3 component n-recognin 5 (UBR5) is a highly conserved member of the homology to E6-AP carboxyl terminus (HECT) E3 ubiquitin protein ligase family that is necessary for cell development [48]. UBR5 plays critical roles in diverse cancers and functions as a regulator of the ubiquitin-proteasome system [48-50]. Recent research has shown that high UBR5 expression levels are related to poor GBC prognosis. UBR5 leads to the ubiquitin-mediated degradation of phosphatase and tensin homolog (PTEN) [51], and UBR5 downregulation is associated with increased PTEN expression. Importantly, PTEN attenuates AKT phosphorylation. UBR5 is known to function as a regulator of BCL-2 and BAX. Therefore, UBR5 knockdown could increase BAX expression and decrease BCL-2 expression, inhibiting tumor growth in GBC. A UBR5-targeted approach may provide another avenue for gallbladder cancer therapeutic and diagnostic strategies [52, 53].

Kinesin family member 11 (KIF11) is a mitotic kinesin necessary for mitotic and cellular movements [54]. KIF11 is highly expressed in GBC and is upregulated by histone acetylation modification in gallbladder cancer [55]. KIF11 could promote cellular proliferation by accelerating the G2/M phase of the cell cycle and activating the ERBB2/PI3K/AKT signaling pathway. Additionally, the KIF11-specific inhibitor monastrol induces G2/M arrest and inhibits cellular proliferation by downregulating the ERBB2/PI3K/AKT pathway [56]. Although research on this topic remains in its infancy and has limitations, the current body of information has increased understanding of the molecular mechanisms underlying gallbladder cancer initiation.

Deleted in malignant brain tumors 1 (DMBT1) is a member of the scavenger receptor cysteine-rich protein family and is known to be involved in mucosal innate immunity [57]. Several studies show that DMBT1 can function as a tumor suppressor due to homologous deletions, and DMBT1 expression is reduced in various cancers relative to normal cells [57-60]. A recent study shows that DMBT1 plays an anticancer role in GBC and is expressed at low levels in GBC tissues. To further study the true function of DMBT1, GBC-SD cells expressing high levels of DMBT1 have been established. In both *in vivo* and *in vitro* experiments, increased DMBT1 expression inhibits cell growth and induces apoptosis. Additionally, DMBT1 overexpression is significantly negatively correlated with p-AKT levels, implying that DMBT1 overexpression may suppress the PI3K/AKT pathway. Furthermore, DMBT1 overexpression upregulates the protein levels of PTEN, which is a known tumor suppressor [59]. Altogether, these studies may provide a new strategy for inhibiting the cancerogenic pathway, downregulating the PI3K/AKT pathway, and promoting the anticancer protein PTEN.

Sparc/osteonectin, cwcv, and kazal-like domains proteoglycan 1 (SPOCK1) is a multidomain protein that is homologous to various protease inhibitors and it helps to regulate the dynamic equilibrium of the extracellular matrix (ECM) [61]. In humans, SPOCK1 is highly expressed in the central nervous system, and SPOCK1 functions are consistent with its distribution pattern in various tissues [62]. Additionally, SPOCK1 is a component and a regulator of the ECM, involved in ECM regression and remodeling, which are vital in tumorigenesis [62]. Abnormal ECM produces molecular cues for cancer occurrence and development, alters cell signaling and microenvironmental cues, and plays a critical role in cancer formation at both primary and metastatic sites [63]. Thus, SPOCK1, which is highly expressed in cancer, contributes to cellular proliferation and promotes cell migration and invasion *in vitro* and *in vivo* by inducing the epithelial to mesenchymal transition (EMT). These effects have been attributed to SPOCK1 activation of the PI3K/AKT pathway. In theory, SPOCK1 knockdown should exhibit an anticancer effect, and studies have shown that SPOCK1 depletion significantly reduces xenograft volume [64]. These results provide supporting evidence that SPOCK1 functions as an oncogene in GBC, and drugs targeting SPOCK1 may yield a novel GBC treatment direction.

Serine threonine tyrosine kinase 1 (STYK1) exhibits abnormal expression levels in diverse cancers [65-67]. STYK1 plays a key role in growth factor membrane receptors and functions as a promotor in cellular proliferation and tumor development [67]. Some studies have reported that STYK1 is highly expressed in GBC tissues and is related to poor GBC prognosis.

STYK1 overexpression upregulates N-cadherin and downregulates the epithelial marker E-cadherin [68], which promotes the EMT [66]. Additionally, STYK1 promotes tumor cell growth and inhibits apoptosis. Furthermore, STYK1 overexpression enhances AKT phosphorylation, whereas STYK1 knockdown reduces AKT phosphorylation, demonstrating that STYK1 exerts an oncogenic effect through the PI3K/AKT pathway. Therefore, an AKT-specific inhibitor has the potential to inhibit STYK1-mediated oncogenic effects in GBC cells. These findings may provide new research directions that may ultimately lead to the discovery of new molecular methods targeting STYK1 in GBC therapy [66].

LIM and SH3 domain protein 1 (LASP-1) is a specific focal adhesion protein that has the ability to promote tumor growth, distant metastasis, and invasiveness in several types of cancer [69]. LASP-1 expression levels are closely associated with tumor size and deterioration, especially in metastatic lymph nodes [70-73]. S100 calcium-binding protein P (S100P), a member of the EF-hand calcium-binding family of S100 proteins, regulates various cellular activities in a Ca^{2+}-dependent manner [74]. LASP-1 and S100P are both overexpressed during GBC-mediated deterioration, and the overexpression of both is associated with poor prognosis. When LASP-1 is downregulated, fewer cell membrane protrusions are observed, and S100P expression also decreases via the PI3K/AKT pathway [75]. Furthermore, when LASP-1 is depleted, cell migration and invasion are both suppressed. Therefore, the targeted reduction of LASP-1 and S100P levels may effectively inhibit aggressiveness and limit the ability of GBC to metastasize. Taspase 1 (TASP1) is another protein associated with invasion and metastasis. *TASP1* is a nonconventional oncogene as it not only regulates the expression of homeotic genes but is also involved in carcinogenesis, suggesting that TASP1 may be a potential target for cancer therapy. TASP1 is highly expressed in GBC tissues and is associated with poor prognosis in GBC patients. Additionally, TASP1 promotes GBC cell proliferation and migration by upregulating itself with sequence similarity 9 member B (FAM49B), a GBC-associated oncoprotein involved in cellular proliferation and metastasis [76]. This study confirmed that the TASP1-PI3K/AKT-FAM49B axis is a novel molecular pathway involved in GBC development and may ultimately lead to significant clinical prospects for GBC treatment [77].

Bromodomain-containing protein 4 (BRD4) is a transcriptional and epigenetic regulator that plays a crucial role in cancer development [78]. Low BRD4 expression occurs in diverse cancers such as gastric cancer [79], breast cancer [80], colorectal cancer [81], and prostate cancer [82]. However, GBC patients have high BRD4 expression levels. Studies show that p-PI3K and p-AKT levels reduce dramatically during BRD4 downregulation, inhibiting cell metastasis, cell proliferation, and tumor growth [78, 83]. When BRD4 expression is upregulated by plasmid transfection into NOZ cell lines and then treated with a PI3K/AKT inhibitor, BRD4 expression in NOZ cells remains elevated, although cell proliferation is reduced, indicating that BRD4 downregulation could function as a tumor suppressor by affecting the PI3K/AKT pathway. Therefore, the development of a BRD4 inhibitor as an antitumor drug has promise for GBC treatment [78].

Every tripartite motif (TRIM) protein promotes ubiquitin-related modifications and transcriptionally silences target genes [84, 85]. Tripartite motif-containing 31 (TRIM31) is a member of the TRIM protein family that has elevated expression and functions as a tumor promoter in GBC [86, 87]. TRIM31 downregulation in GBC cells was accompanied by low expression of matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9). Furthermore, overexpression of MMP2/9 leads to ECM deregulation, allowing for the invasion of tumor cells in other organs and metastasis to distant tissues [88, 89]. Thus, low TRIM31 expression can suppress invasion and distant metastasis by downregulating MMP2/9 through the PI3K/AKT pathway [90]. Taken together, targeting TRIM31 is a potential avenue for treating the highly invasive distant metastases associated with GBC.

Inositol polyphosphate 4-phosphatase type II (*INPP4B*), a dual-function cancer regulator gene that is well-known to negatively regulate the PI3K/AKT pathway, has received increasing interest [91, 92]. INPP4B expression differs in different cancers, with high expression levels reported in acute myeloid leukemia and

colorectal carcinoma and decreased expression in GBC [93]. Surprisingly, this contradictory role has been found even within the same cancer types, including GBC [94]. High expression of INPP4B results in a better prognosis in the high differentiation group, but high INPP4B expression often leads to a worse outcome in the low differentiation group [95]. These results emphasize the paradox of INPP4B expression for GBC outcomes associated with different degrees of histopathological differentiation. Therefore, further study is required to confirm the mechanism of action through which INPP4B affects GBC.

Fundamentals and expectations of chemotherapeutics

GBC is a common biliary tract carcinoma, typically associated with poor prognosis [14, 96, 97]. Current treatment options, such as operative treatment, chemotherapeutics, and radiotherapy, each have diverse limitations [14, 98, 99]. Treatments for GBC patients are mostly dependent on surgery, but major concerns include early local metastasis and postoperative recurrence, even after complete resection [98].

Therefore, it is necessary and urgent to discover new therapeutic strategies to treat GBC. The PI3K/AKT pathway is crucial to the occurrence and development of cancers, affecting cell proliferation, migration, invasion, cell cycle, and apoptosis in GBC progression [100, 101]. Additionally, the PI3K/AKT pathway has great potential to be targeted by a therapeutic approach (**Table 3**).

When the combined effects of two or more drugs that act in the same direction result in a total effect that is greater than the sum of the individual effects attributed to each drug, these drugs are described as having synergistic effects. Commonly used drugs in combination chemotherapy strategies include afatinib or regorafenib, cetuximab or erlotinib, and sorafenib or bevacizumab [98]. However, chemotherapy treatments for GBC have revealed evident drug resistance and insensitivity [100]. The combined use of some drugs represents an attractive method for improving clinical efficacy. Phenoxodiol (PXD), an isoflavene antitumor agent [102], sensitizes GBC cells to gemcitabine, and the combination of gemcitabine and PXD can kill more GBC-SD cells than treatment with either gemcitabine or PXD alone. The combination of PXD and gemcitabine results in improved sensitization to apoptosis, induced G0/G1 arrest, and enhanced antitumor effects. PXD inhibits the AKT signaling pathway, causing the downregulation of apoptosis-related genes and sensitizing cells to gemcitabine-induced apoptosis [103]. The BRD4 inhibitors JQ1 and suberoylanilide hydroxamic acid (SAHA) can also be used as anticancer agents. An *in vitro* study in GBC cells showed that combining JQ1 and SAHA enhances the loss of cell viability, induction of apoptosis, and G2/M phase cell cycle arrest. Either JQ1 or SAHA alone can reduce tumor volumes and weights in GBC xenograft models, but their combination exerts the strongest curative results. Additionally, the anticancer activities of JQ1 and SAHA are connected through their abilities to decrease expression of BRD4, inhibiting the PI3K/AKT pathway. These findings highlight the combination of JQ1 and SAHA as a promising potential therapeutic strategy for treating GBC [83].

The first-line therapeutic regimen for GBC patients with terminal stage or concurrent distant metastasis is the combination of gemcitabine and cisplatin (Cis). Although this combination has anticancer effects, the median overall survival remains shorter than 1 year [104]. Metformin (Met), an extensively used antidiabetic drug, has recently been reported to exhibit anticancer activity in diverse cancer models, either alone or in combination with others chemotherapeutics [105]. A study revealed that Met acts synergistically with cis, enhancing antiproliferative activity and cis-induced apoptosis in human GBC cells. These results suggest that the combination of Met and Cis functions synergistically in GBC cells through the PI3K/AKT/ERK pathway, exerting antitumor properties. This combination treatment regimen may serve as a new GBC patient treatment strategy [106].

In addition to combination therapy, flavonoids also have excellent anticancer properties through the upregulation of factors that suppress cancer. Oroxylin A (OrA) is a natural flavonoid that exerts anti-inflammatory and antitumor properties on different cancer types [107-109]. Flavonoids exhibit anticancer activity in

Table 3. The following chemotherapy agents, either in combination or alone, inhibit the occurrence and development of GBC through crosstalk with the PI3K/AKT pathway

Chemotherapeutic agent	Pathway	Function in vivo	Function in vitro	Prognosis	Reference
Pterostilbene	Inhibit PI3K/AKT pathway	Inhibit the formation of GBC xenografts	Inhibit the proliferation, migration and invasion; Induce apoptosis; Reverse EMT	Ameliorative	[123]
Isorhamnetin	Inhibit PI3K/AKT pathway	Inhibit tumor growth	Inhibit the proliferation; migration and invasion; Induce apoptosis; Triggers cell cycle arrest in the G2/M Phase	Ameliorative	[119]
Metformin enhances Cisplatin	Inhibit PI3K/AKT/ERK pathway	Improve the anti-tumor effect	Enhance the anti-proliferative effect, and Cis-induced apoptosis; Induce G0/G1 phase arrest	Ameliorative	[107]
Phenoxodiol enhances Gemcitabine	Suppress AKT/mTOR Pathway	Potentiate the Antitumor Effect	Loss of cell viability; Sensitize apoptosis induced by Gemcitabine; Potentiate Gemcitabine-Induced G0/G1 Arrest	Ameliorative	[104]
Sinensetin flavone	Suppress PTEN/PI3K/AKT pathway	/	Inhibit cell viability/proliferation migration and cell invasion; Apoptosis induction	Ameliorative	[117]
Oroxylin A	Inhibit PTEN/PI3K/ AKT Pathway	Suppress the growth of Xenografts	Inhibit cells proliferation, migration and invasion; Promote apoptosis	Ameliorative	[112]
Liensinine	Inhibit ZFX-induced PI3K/AKT pathway	Inhibit the volumes and weights of the tumors	Inhibit proliferation; Induce G2/M arrest	Ameliorative	[136]
Dioscin	Inhibit ROS-Mediated PI3K/AKT pathway	Inhibit tumor growth	Inhibit proliferation and migration; Induce cell apoptosis	Ameliorative	[102]
Bufalin	Inhibit MEK/ERK and PI3K/AKT Pathways	Suppress xenografted tumor growth	Suppress proliferation invasion and migration; Induce apoptosis and cell cycle arrest	Ameliorative	[101]
BRD4 inhibitor and histone deacetylase inhibitor	Suppress PI3K/AKT and MAPK/ERK pathways	Decrease tumor volumes and weights	Inhibit proliferation, cell viability and metastasis; Induce apoptosis and G2/M arrest	Ameliorative	[83]

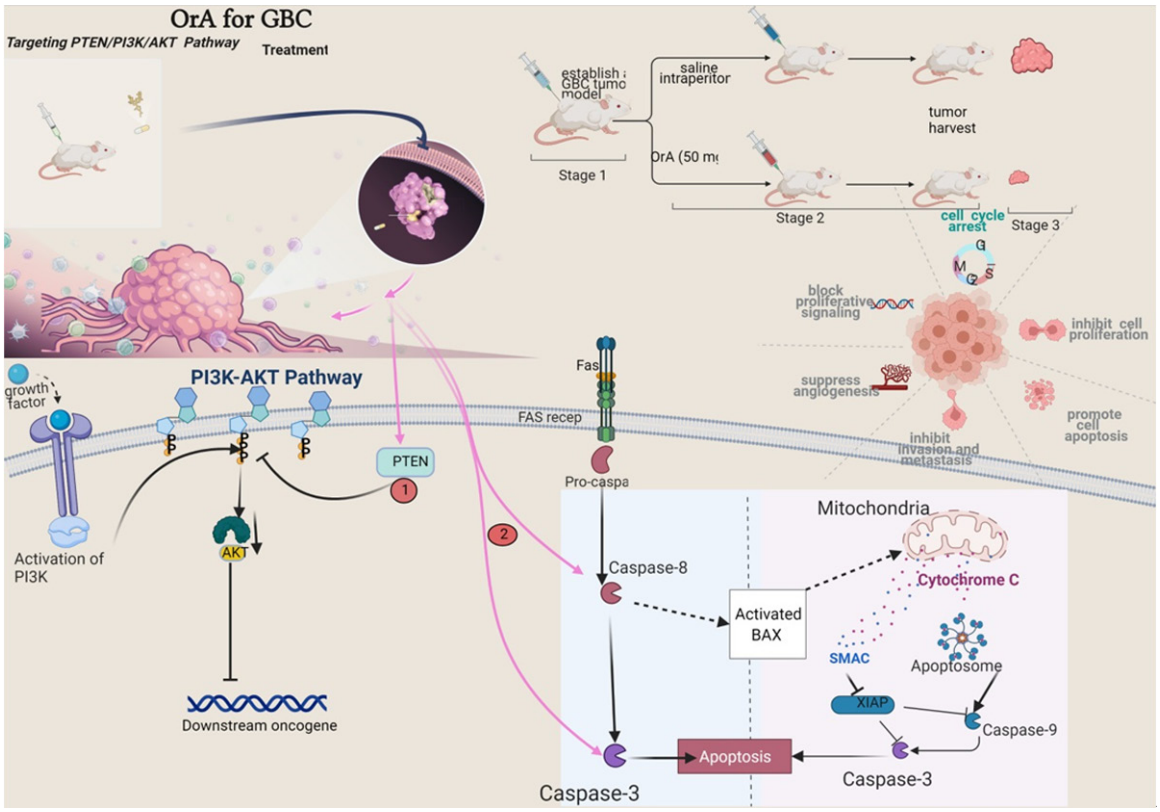

Figure 2. OrA is a Chinese herbal extract that can have an anticancer effect by upregulating PTEN and decreasing AKT. In *in vivo* experiments using a rat model of GBC compared two groups, one injected with saline and one injected with OrA. The results suggested that the OrA treatment group showed suppressed tumor growth compared with the control group. *In vitro*, OrA inhibits cellular proliferation, promotes apoptosis, and inhibits cell migration and invasion. Furthermore, OrA treatment increases the expression levels of caspase-3 and caspase-8 in a dose-dependent manner to cause apoptosis by promoting mitochondrial apoptosis.

various ways, such as regulating the activities of reactive oxygen species (ROS)-scavenging enzymes, inducing cell apoptosis, and inhibiting cancer cell proliferation and invasion [110]. Results from *in vitro* experiments suggest that OrA inhibits cellular proliferation, promotes apoptosis, and inhibits cell migration and invasion. Further studies showed that OrA treatment could suppress tumor growth volume and weight compared with the control group. OrA exerts anticancer activity by upregulating PTEN expression and inhibiting AKT expression, modulating the PTEN/PI3K/AKT pathway [111] (**Figure 2**). PTEN, an effective tumor suppressor, is a membrane-bound protein phosphatase that primarily targets PIP3. Low PTEN expression results in the excessive activation of the PI3K/AKT pathway, accelerating cell growth and increasing survival [112]. Additionally, drugs targeting the PTEN/PI3K/AKT signaling pathway can slow tumor progression [113, 114]. In recent years, the PTEN/PI3K/AKT pathway has become a target of increasing interest for medicinal development and treatment in GBC patients [106].

Sinensetin (SIN) is a polymethoxylated flavonoid that has been shown to manifest a number of biological functions, including anti-inflammatory and anticancer properties [115]. Research shows that SIN inhibits GBC cell viability and proliferation by inducing apoptosis and inhibiting cell migration and invasion by decreasing MMP2/9. Furthermore, SIN also functions as a tumor suppressor by targeting and blocking the PTEN/PI3K/AKT pathway [116]. In conclusion, the flavonoid derivatives OrA and SIN have the potential to serve as therapeutics that target GBC cells.

Another flavonoid chemical compound, isorhamnetin, has a special chemical composition

that enables it to exert numerous pharmacological effects, including anti-inflammatory, antitumor, and antiviral effects [117]. Furthermore, studies show that isorhamnetin inhibits proliferation, suppresses migration and invasion, induces apoptosis, and triggers cell cycle arrest in the G2/M phase when used to treat GBC cells. Isorhamnetin exerts these antitumor effects by downregulating the PI3K/AKT pathway [118]. Pterostilbene (PTS) is a phytoalexin that represents a great example of a natural plant defense molecule that has been developed into an anticancer chemotherapeutic agent for human oncotherapy [119, 120]. Experimental evidence indicates that the special molecular composition of PTS endows it with greater bioavailability than resveratrol, which allows it to exhibit effective anticancer characteristics [121]. These anticancer properties conferred by PTS on GBC are the result of PI3K/AKT pathway inhibition and include inhibiting proliferation, inducing apoptosis, inhibiting migration and invasion, and reversing EMT. Additionally, PTS can inhibit the formation of GBC xenografts *in vivo* [122].

Chemotherapeutic agents that reduce oncogene expression can also suppress cancer progression. For example, mesenchymal-epithelial transition factor (c-Met) is the protein product of the *MET* proto-oncogene, and it has been associated with cell invasion and metastasis by directly regulating tumor angiogenesis [123]. Overexpression of c-Met has been associated with poor GBC patient prognosis, indicating the potential for c-Met as a therapeutic target [124, 125]. Bufalin is a cardiotonic steroid and a highly active toxic compound that also has pharmaceutical value as an anti-inflammatory and anticancer therapeutic [126-128]. Relevant studies show that bufalin inhibits the xenografted growth of GBC *in vitro*, suppressing cell proliferation, inducing cell cycle arrest, and hindering GBC cell invasion. The anticancer properties of bufalin are due to its ability to inhibit c-Met, which inhibits the PI3K/AKT pathway [100, 124]. Previous research has shown that zinc finger protein X-linked (ZFX) is highly expressed in malignancies, such as hepatocellular carcinoma [129], prostate cancer [130], breast cancer [131] and GBC [132], indicating that ZFX plays a significant role in these cancers and implying that inhibiting ZFX-mediated pathways could suppress cancer progression [133, 134]. Furthermore, ZFX may function as a prognostic marker or therapeutic target for GBC. Liensinine is a chemical compound that suppresses the PI3K/AKT pathway, inhibiting cell proliferation, inducing G2/M arrest, and promoting cell apoptosis [135]. Further studies revealed that ZFX expression is reduced after liensinine treatment, which indicates that liensinine may be an effective chemotherapeutic agent against GBC. ROS are a class of highly active molecules that induce DNA damage and influence the related DNA-damage response. Explicit clinical evidence shows that ROS affect genotoxic stress caused by chemotherapeutics and radiation [136]. Furthermore, ROS activate cancer-related cellular activities, such as cell proliferation, apoptosis, migration, and invasion. Thus, the importance of ROS in cancer has led to the clinical assessment of ROS-regulating agents in cancers, which has had mixed success [137]. Dioscin (DSN), a plant glucoside saponin, has been shown to exert many biological and pharmacological effects, such as anticancer, anti-inflammatory, and antiviral effects. DSN has attracted increasing attention due to its therapeutic activity in lung cancer, colorectal carcinoma, and gastric cancer [138]. Furthermore, it has been shown that DSN inhibits the PI3K/AKT signaling pathway by regulating ROS. Additionally, DSN treatment in GBC cells inhibits proliferation and induces apoptosis, including mitochondrial-dependent apoptosis.

Conclusions and perspectives

Although the global incidence of GBC is relatively low, it is extremely malignant and highly fatal. Due to the asymptomatic nature of early-stage GBC and a high propensity for distant metastasis, patients are typically diagnosed at a terminal or progressive stage, with no available curative treatment, leading to poor prognosis and a low survival rate [3]. In spite of significant progress that has been made in GBC therapeutic regimens, therapeutic approaches continue to be limited in their curative abilities [96, 139, 140]. Therefore, discovering new uses for agents known to target metastasis is an increasingly popular strategy for treating GBC. The PI3K/AKT pathway is known to affect many cellular activities following activation, promoting the advancement of diverse cancers, including GBC [18, 141-143]. Increasing

evidence demonstrates the significant role of the PI3K/AKT pathway in the occurrence and development of GBC, as the upregulation and activation of the pathway itself are signs of cancer. Thus, targeting the PI3K/AKT pathway could ultimately be an effective method for treating GBC. Further clarification regarding the activation and regulation of the PI3K/AKT pathway will yield new research directions and therapeutic strategies not only for GBC patients but also for patients with other cancers [118, 144]. The molecules and proteins described in this review could be used as early markers and therapeutic targets to detect gallbladder cancer at earlier stages than current methods and provide enhanced therapeutic activity at an early stage. Furthermore, these described compounds and drugs may prove to be more effective at treating cancer, ultimately improving gallbladder cancer patient prognosis.

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Disclosure of conflict of interest

None.

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