Long non-coding RNA GAS6-AS1 and its molecular mechanisms in human cancer (Review)

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Received June 3, 2026; Accepted August 25, 2026

DOI: 10.3892/br.2026.2200

Abstract. Long non-coding RNAs (lncRNAs) play crucial roles in regulating gene expression and tumor progression. Growth arrest specific 6-antisense RNA 1 (GAS6-AS1), a novel lncRNA located antisense to the GAS6 gene, has been increasingly recognized as an important regulator in multiple cancers. Emerging evidence demonstrates that GAS6-AS1 participates in tumor initiation and progression by functioning as a competitive endogenous RNA that modulates microRNA activity, regulates downstream target genes, and influences key signaling pathways, including Wnt/β-catenin and AXL signaling. Through these mechanisms, GAS6-AS1 affects cancer cell proliferation, migration, invasion, apoptosis, metabolic reprogramming and chemoresistance. GAS6-AS1 exhibits context-dependent functions across different cancer types. GAS6-AS1 predominantly functions as an oncogenic lncRNA in multiple cancers, including colorectal cancer, breast cancer, hepatocellular carcinoma, ovarian cancer, glioma, gastric cancer, renal cell carcinoma and acute myeloid leukemia. In contrast, GAS6-AS1 has been reported to exert tumor-suppressive effects in lung adenocarcinoma. Abnormal expression of GAS6-AS1 is closely associated with tumor progression, metastasis and patient prognosis, highlighting its potential as a diagnostic and prognostic biomarker as well as a therapeutic target. Overall, GAS6-AS1 represents a promising molecule for understanding cancer pathogenesis and developing novel strategies for precision cancer diagnosis and treatment, although further clinical validation and mechanistic studies are still required.

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Key words: lncRNA, GAS6-AS1, cancer progression, ceRNA, microRNA regulation, tumor biomarker, signaling pathways

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1. Introduction

Increasing evidence indicates that long non-coding RNAs (lncRNAs) play diverse roles in multiple stages of normal cellular biology and pathological processes (1). LncRNAs are transcripts exceeding 200 nucleotides in length that cannot encode proteins due to the absence of open reading frames (2). Unlike traditional messenger RNAs, lncRNAs do not primarily function through protein translation, but instead regulate gene expression and cellular behavior through diverse molecular mechanisms. It has been shown that lncRNAs participate in chromatin remodeling, transcriptional regulation,

post-transcriptional processing, RNA stability and protein modification, thereby influencing multiple physiological and pathological processes (3). In recent years, with the rapid development of high-throughput sequencing technologies and bioinformatics analysis, researchers have identified numerous lncRNAs associated with human diseases, especially malignant tumors. Cancer remains one of the leading causes of death worldwide, and despite considerable progress in diagnosis and treatment, the prognosis of numerous advanced malignancies remains unsatisfactory. Tumor initiation and progression involve complex interactions among oncogenes, tumor suppressor genes, signaling pathways and the tumor microenvironment. Increasing studies have confirmed that lncRNAs are deeply involved in tumorigenesis, metastasis, therapeutic resistance, immune escape and metabolic reprogramming. Therefore, lncRNAs have attracted extensive attention as novel biomarkers and therapeutic targets.

Growth arrest-specific 6 antisense RNA 1 (GAS6-AS1) is an lncRNA located on chromosome 13q34 and transcribed antisense to the GAS6 gene. It comprises five exons and produces a transcript of ~902 nucleotides. As an antisense transcript, GAS6-AS1 can regulate its cognate sense gene GAS6 by forming an RNA-RNA duplex, thereby modulating GAS6 expression and downstream AXL signaling in a context-dependent manner. In addition to this GAS6-dependent mechanism, GAS6-AS1 can also function independently through competitive endogenous (ce)RNA networks and interactions with RNA-binding proteins or transcription factors (4). Emerging evidence indicates that GAS6-AS1 participates in regulating proliferation, migration, invasion, epithelial-mesenchymal transition (EMT), glycolysis and drug resistance in various tumors (4-8). Furthermore, GAS6-AS1 exhibits cancer-type-specific biological functions. In most malignancies, GAS6-AS1 functions as an oncogenic lncRNA that promotes tumor progression, whereas in lung adenocarcinoma (LUAD), it may exhibit tumor-suppressive properties. In addition, abnormal expression of GAS6-AS1 is significantly associated with clinicopathological characteristics, including tumor stage, lymph node metastasis, recurrence and overall survival. Therefore, GAS6-AS1 may serve not only as a molecular biomarker for early tumor diagnosis and prognosis prediction, but also as a promising target for precision therapy. Currently, the mechanisms underlying GAS6-AS1-mediated tumor progression are being gradually elucidated. GAS6-AS1 can function as a ceRNA by sponging tumor-suppressive micro (mi)RNAs and regulating downstream target genes. It can also interact with RNA-binding proteins and transcription factors to modulate signaling pathways involved in tumor development. These pathways include Wnt/β-catenin signaling, AXL signaling and glucose metabolic pathways. Through these mechanisms, GAS6-AS1 influences multiple malignant phenotypes of tumor cells. In particular, studies have revealed additional roles of GAS6-AS1 in chemoresistance and complex ceRNA- and RNA-binding protein-mediated regulatory networks, further highlighting the need for an updated and focused synthesis of this lncRNA (4,9). Therefore, this review specifically summarizes current evidence regarding the aberrant expression, biological functions, molecular regulatory networks and clinical significance of GAS6-AS1 across different cancers. Its potential value as a diagnostic and prognostic biomarker and therapeutic target were also discussed, as well as current challenges and future directions for its clinical translation.

2. Characteristics of lncRNA GAS6-AS1

LncRNAs play crucial roles in regulating gene expression at both the transcriptional and post-transcriptional levels (9,10). Previous studies have demonstrated that lncRNAs can exert either tumor-suppressive or oncogenic effects through diverse mechanisms, including molecular sponging and post-transcriptional regulation (11-16). Importantly, their tissue- and context-specific expression patterns make lncRNAs attractive candidates for cancer diagnosis and prognosis evaluation. GAS6-AS1 is a recently identified cancer-associated lncRNA that plays important roles in malignant tumors and may serve as a potential biomarker for cancer diagnosis and prognosis (5). GAS6-AS1 is located on chromosome 13q34 and transcribed antisense to the GAS6 gene. It has five exons and generates one variant transcript, which is composed of a 902-nt lncRNA (Fig. 1) (4). To investigate the secondary structure of lncRNA GAS6-AS1 in depth, this study utilized the ViennaRNA Web Services (http://rna.tbi.univie.ac.at/forna/) to visualize it using RNA secondary structure prediction and visualization analysis (Fig. 2). Subcellular localization analysis revealed an apparent discrepancy among different prediction platforms. lncLocator (http://www.csbio.sjtu.edu.cn/bioinfo/lnclocator/) predicted that GAS6-AS1 is preferentially localized in the cytoplasm (score: 0.688; Table I), whereas lncATLAS (http://lncatlas.crg.eu/) analysis based on RNA-sequencing data from multiple human cell lines indicated relative nuclear enrichment. This inconsistency may arise from differences in the underlying analytical strategies. lncLocator is an integrated machine-learning prediction tool based on sequence-derived features, whereas lncATLAS reflects experimentally generated RNA-sequencing profiles from specific cellular contexts. Therefore, the predicted localization of GAS6-AS1 may not represent a universal characteristic but rather a context-dependent pattern influenced by cell type, tumor origin, differentiation state and intracellular regulatory environment. Consistent with this concept, experimental studies have reported diverse subcellular distributions of GAS6-AS1. In LUAD cells, GAS6-AS1 was predominantly detected in the nucleus, where it interacted with the transcription factor E2F1 to regulate glucose transporter 1 (GLUT1) transcription (6). By contrast, studies in colorectal cancer (CRC) and acute myeloid leukemia (AML) demonstrated that GAS6-AS1 was distributed in both nuclear and cytoplasmic compartments, enabling distinct regulatory mechanisms, including miRNA sponging and RNA-binding protein-mediated regulation (5,7). These findings suggest that GAS6-AS1 does not possess a fixed subcellular localization; instead, its intracellular distribution may determine its functional mode in different tumor contexts (Fig. 3). Cytoplasmic enrichment may facilitate ceRNA-mediated post-transcriptional regulation, whereas nuclear localization may support transcriptional regulation or interactions with nuclear RNA-binding proteins. Further experimental validation using cell-type-specific fractionation and imaging approaches is required to fully define the dynamic localization landscape of GAS6-AS1. Structural analysis of

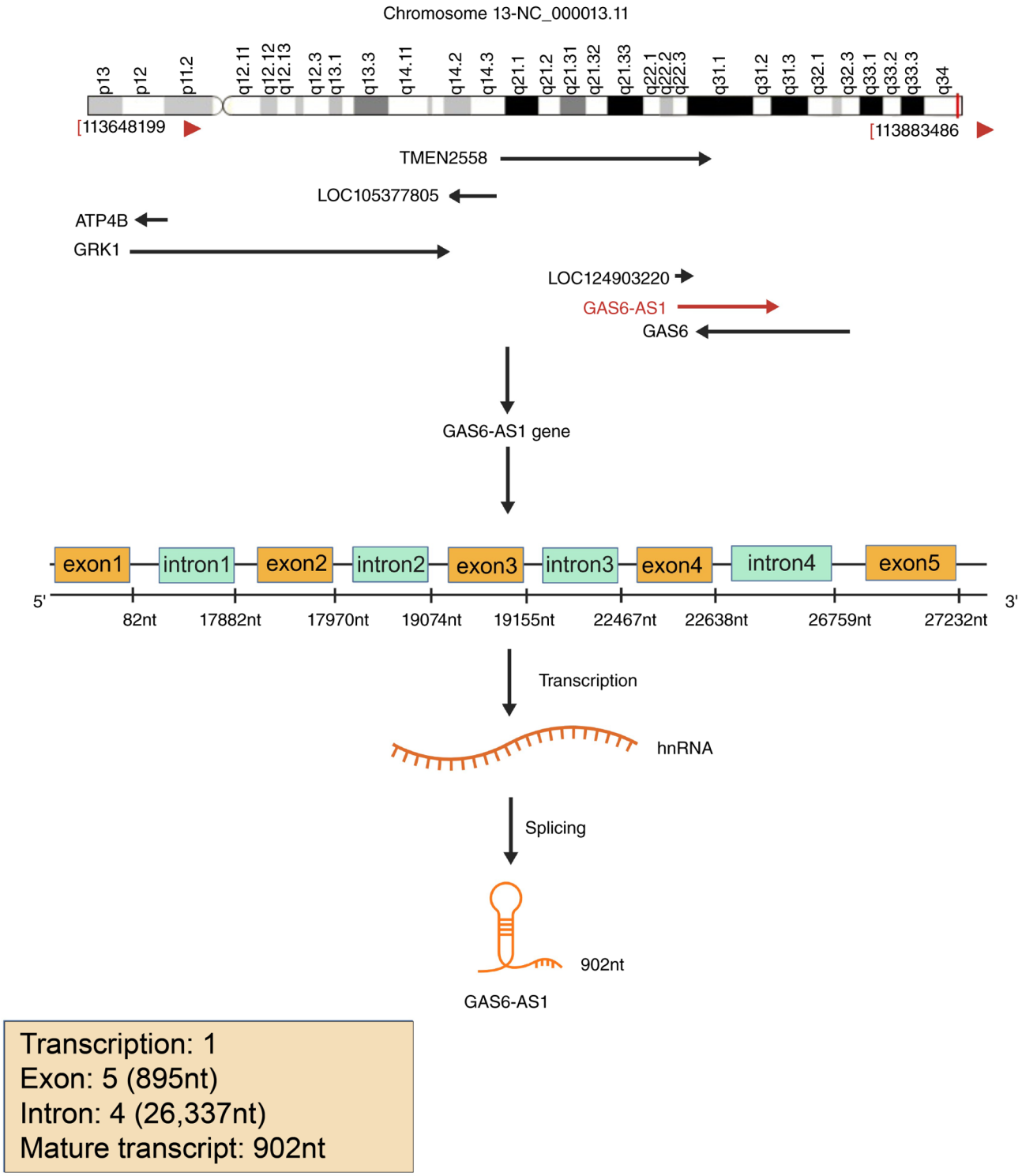

Figure 1. Chromosomal localization and transcript structure of long noncoding RNA GAS6-AS1. GAS6-AS1 is located at chromosome 13q34 and is transcribed in an antisense direction relative to the protein-coding gene GAS6. The genomic locus of GAS6-AS1 is shown together with adjacent genes and transcriptional orientation. GAS6-AS1 contains five exons separated by four introns and produces a mature transcript of ~902 nucleotides following splicing. This schematic illustrates the genomic organization and structural features of GAS6-AS1. hnRNA, heterogeneous nuclear RNA; GAS6, growth arrest specific 6; AS1, antisense 1.

lncRNAs is important because their biological functions are closely associated with their secondary and tertiary structures, which influence their interactions with RNA-binding proteins and other nucleic acids. GAS6-AS1 regulates GAS6 levels at the transcriptional or translational level, thereby increasing AXL expression in a tumor-context-dependent manner and activating the AXL signaling pathway. GAS6 is a vitamin K-dependent protein and a high-affinity ligand for the AXL receptor tyrosine kinase (17). Structurally, GAS6 comprises a γ-carboxyglutamic acid domain, four epidermal growth factor-like domains and two laminin G-like domains (18). The GAS6/AXL signaling axis regulates multiple cancer-related

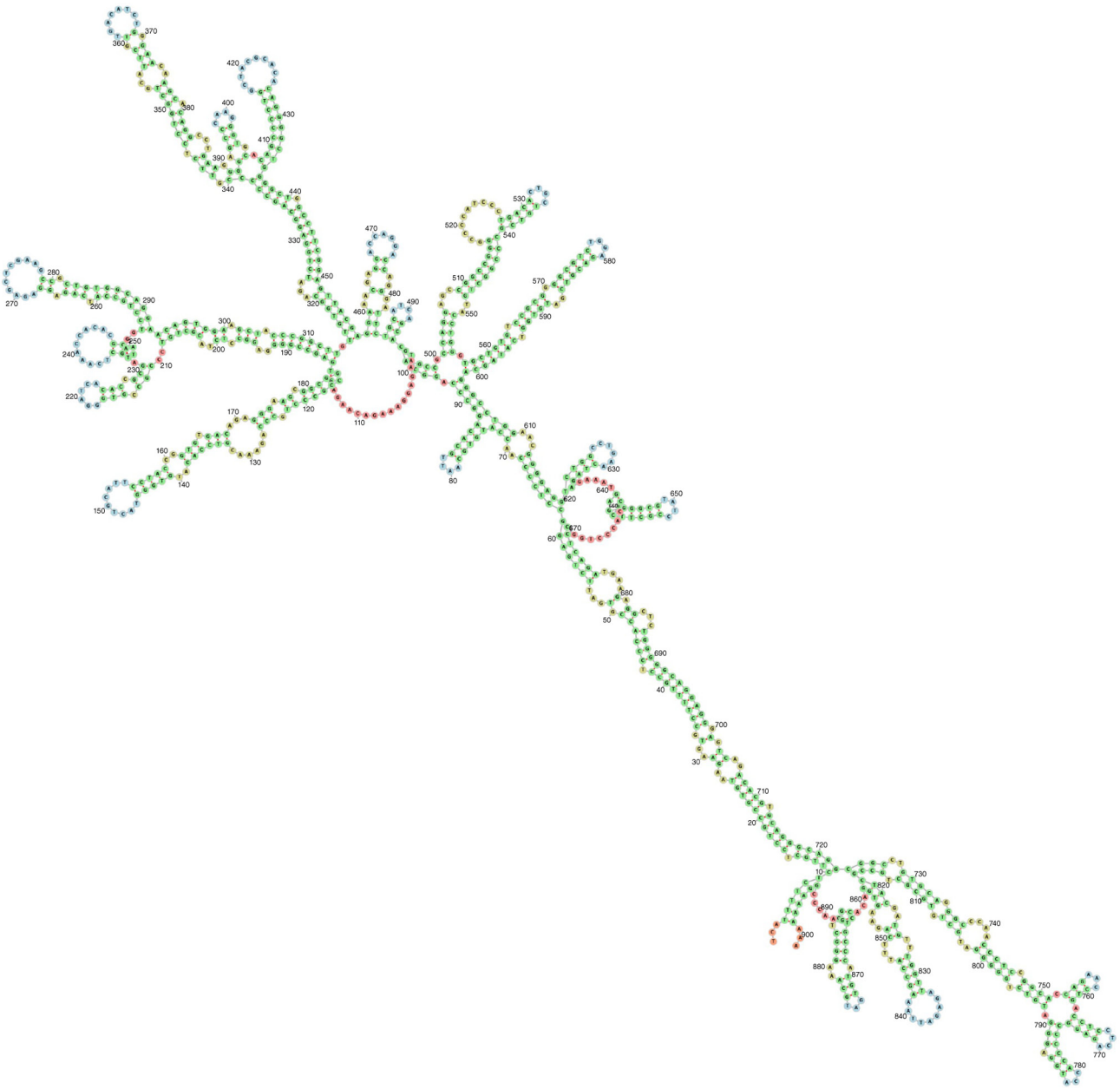

Figure 2. Predicted secondary structure of GAS6-AS1. The secondary structure of the 902-nucleotide GAS6-AS1 transcript was predicted and visualized using FORNA (ViennaRNA Web Services; http://rna.tbi.univie.ac.at/forna/) based on the GAS6-AS1 sequence obtained from the NCBI database (https://www.ncbi.nlm.nih.gov/gene/642934). Nucleotides are numbered according to their positions along the transcript, illustrating the predicted stem-loop and branching structural features of GAS6-AS1. The nucleotides are colored according to their structural context: green indicates stems (canonical helices), red indicates multiloops (junctions), yellow indicates interior loops/bulges, blue indicates hairpin loops, and orange indicates unpaired terminal regions. The numbers indicate nucleotide positions along the RNA sequence. NCBI, National Center for Biotechnology Information; ATP4B, ATPase H+/K+ transporting subunit beta; GRK1, G protein-coupled receptor kinase 1; GAS6, growth arrest specific 6; AS1, antisense 1.

processes, including cell proliferation, migration, apoptosis, angiogenesis, immune regulation and drug resistance (19), suggesting that GAS6-AS1 may influence tumor progression through modulation of GAS6. Current evidence indicates that GAS6-AS1 participates in cancer pathogenesis through both GAS6-dependent and GAS6-independent mechanisms (20). In GAS6-dependent mechanisms, GAS6-AS1 regulates the expression and activity of GAS6 and subsequently activates downstream signaling pathways. By contrast, GAS6-independent mechanisms involve the ceRNA network, transcriptional regulation and interactions with RNA-binding proteins. These diverse mechanisms explain the broad functional spectrum of GAS6-AS1 in different tumor types. An analysis using the Gene Expression Profiling Interactive Analysis (GEPIA) online database (http://gepia.cancer-pku.cn/) revealed that the expression of GAS6-AS1 varies significantly across several cancers (Fig. 4). LncRNA GAS6-AS1 is overexpressed in numerous human cancers and represents a promising candidate among tumor-associated lncRNAs. Its expression pattern varies across tumor tissues and cell lines, suggesting that GAS6-AS1 may have context-dependent biological functions. Furthermore, the association between GAS6-AS1 expression and clinicopathological characteristics indicates that it may serve as a clinically valuable biomarker.

Table I. Subcellular localization analysis of long non-coding RNA GAS6-AS1.

Subcellular localization	Score
Cytoplasm	0.688319929936
Nucleus	0.199331092194
Ribosome	0.0204750616244
Cytosol	0.0678368378585
Exosome	0.0240370783871

The predicted location of GAS6-AS1 is the cytoplasm. GAS6-AS1, growth arrest-specific 6 antisense RNA 1.

3. Mechanism of action of lncRNA GAS6-AS1 in tumors

LncRNA GAS6-AS1 regulates tumor initiation and progression primarily through functioning as a ceRNA that modulates miRNA activity and downstream signaling pathways. According to the ceRNA hypothesis, lncRNAs can competitively bind miRNAs through miRNA response elements, thereby preventing miRNAs from suppressing their target mRNAs. Through this mechanism, GAS6-AS1 indirectly regulates the expression of multiple oncogenes and tumor suppressor genes. In multiple malignancies, GAS6-AS1 promotes cancer cell proliferation, migration, invasion, EMT and tumor growth by sponging tumor-suppressive miRNAs, including miR-370-3p, miR-1296-5p, miR-215-5p, miR-585 and miR-324-3p, thereby upregulating target genes such as tripartite motif-containing 14 (TRIM14), SRY-box transcription factor 9 (SOX9), eukaryotic translation initiation factor 5A2 (EIF5A2), tetraspanin 3 (TSPAN3) and spermatogenesis associated 2 (SPATA2). By contrast, in LUAD, GAS6-AS1 functions as a tumor suppressor through the GAS6-AS1/miR-24-3p/GTPase of the immune-associated nucleotide-binding protein family member 6 (GIMAP6) axis, where GAS6-AS1 sponges miR-24-3p and increases GIMAP6 expression, thereby suppressing tumor progression (21). Additionally, GAS6-AS1 can interact with RNA-binding proteins to enhance mRNA stability and activate oncogenic signaling pathways, such as the Wnt/β-catenin pathway. Notably, the biological effects of GAS6-AS1 are highly context dependent and are determined by the specific downstream regulatory networks engaged in different tumor settings. This functional diversity highlights the complexity of GAS6-AS1-mediated regulation in cancer biology. This dual role highlights the complexity of lncRNA-mediated regulation in cancer biology. Collectively, GAS6-AS1 influences tumor progression through miRNA-mediated regulatory networks and represents a potential biomarker and therapeutic target across diverse cancers (Fig. 5, Table II).

ceRNA-dependent networks of GAS6-AS1

GAS6-AS1 and CRC. CRC is among the most commonly diagnosed malignancies worldwide and represents a major cause of cancer-related mortality according to GLOBOCAN 2022 (22). The incidence of CRC has been increasing steadily in recent decades due to changes in dietary habits, lifestyle, obesity and population aging. CRC lacks distinct clinical manifestations, so most patients are diagnosed at an advanced stage, resulting in poor survival outcomes, particularly among patients diagnosed at advanced stages (23). Therefore, identifying novel molecular biomarkers and therapeutic targets is particularly important for improving patient outcomes. Chen *et al* (5) found that GAS6-AS1 is upregulated in CRC and positively correlates with tumor progression and poor prognosis. High GAS6-AS1 expression is associated with larger tumor size, lymph node metastasis, advanced TNM stage and shorter survival time. Functional studies demonstrated that GAS6-AS1 regulates the proliferation, migration, invasion and EMT of CRC cells *in vitro*, while inducing the growth and metastasis of CRC *in vivo (*5). EMT is a crucial biological process during tumor metastasis, and GAS6-AS1 appears to contribute significantly to this process. Experimental validation confirms that GAS6-AS1 exerts its oncogenic function by competitively binding to miR-370-3p and miR-1296-5p, thereby elevating TRIM14 expression. TRIM14 is an important regulator involved in innate immunity, cell proliferation and tumor progression. Both GAS6-AS1 and TRIM14 interact with fused in sarcoma (FUS), and GAS6-AS1 stabilizes TRIM14 mRNA by recruiting FUS. These findings suggest that GAS6-AS1 not only regulates gene expression through ceRNA mechanisms but also modulates mRNA stability through RNA-binding proteins. Overall, the GAS6-AS1/miR-370-3p/miR-1296-5p/TRIM14 regulatory network plays a crucial role in CRC progression. These findings suggest that GAS6-AS1 may serve as a novel biomarker and therapeutic target for CRC.

GAS6-AS1 and LUAD. Lung cancer represents a major global cancer burden and was the most frequently diagnosed cancer and the leading cause of cancer-related death worldwide in 2022, with ~2.5 million new cases and 1.8 million deaths (22). Non-small cell lung cancer (NSCLC) can be further classified into LUAD and lung squamous cell carcinoma (24). In recent years, the incidence of LUAD has been on the rise. Although advances in surgery, targeted therapy, immunotherapy, radiotherapy and chemotherapy have improved clinical outcomes, the overall survival rate remains <25% (25). Wang *et al* (21) found that GAS6-AS1 was significantly downregulated in all LUAD cell lines. Patients with low GAS6-AS1 expression exhibited poorer overall survival. Overexpression of GAS6-AS1 inhibited cell proliferation, migration and invasion while promoting apoptosis *in vitro*. GAS6-AS1 overexpression also suppressed tumor progression. These findings indicate that GAS6-AS1 functions as a tumor suppressor in LUAD, which differs from its oncogenic role in many other cancer types. To elucidate the functional mechanism of GAS6-AS1 in LUAD, researchers employed bioinformatics analysis to identify an interaction between miR-24-3p and GAS6-AS1. Furthermore, miR-24-3p was found to target GIMAP6 in LUAD cells. GIMAP6 participates in immune regulation and cell survival. GAS6-AS1 may therefore suppress tumor progression through the miR-24-3p/GIMAP6 axis. These results suggest that restoration of GAS6-AS1 expression may represent a promising therapeutic strategy for LUAD. Consequently, GAS6-AS1 may represent a potential diagnostic biomarker and therapeutic target for LUAD.

GAS6-AS1 and breast cancer (BRCA). BRCA is one of the most prevalent malignancies worldwide and represents the most commonly diagnosed cancer among women.

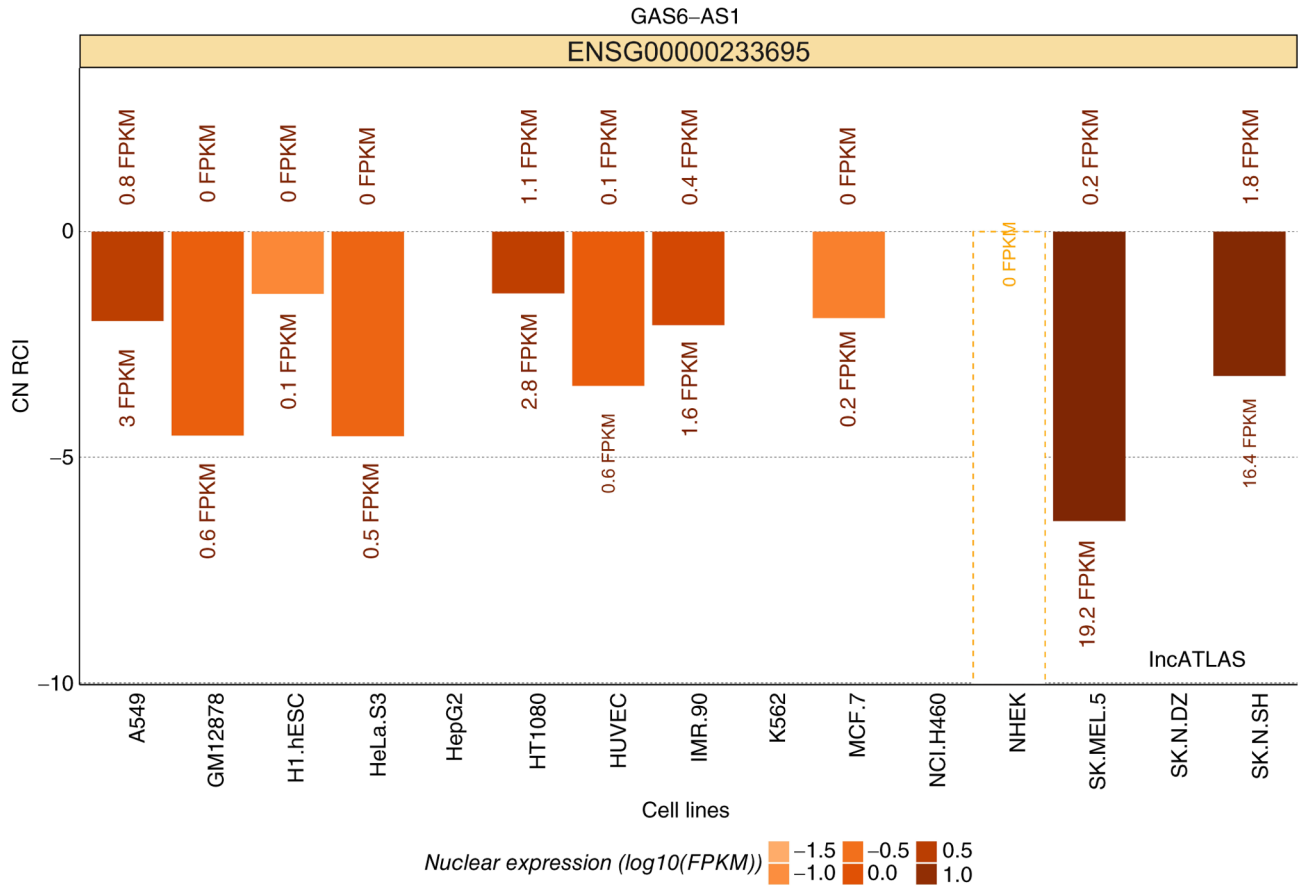

Figure 3. Cell type- and tumour context-dependent subcellular localization of GAS6-AS1. The subcellular distribution of GAS6-AS1 (ENSG00000233695) was analyzed using data from lncATLAS (bar plot from lncATLAS analysis; https://lncatlas.crg.eu/). CN RCI values are shown for the indicated cell lines, with negative CN RCI values indicating preferential nuclear enrichment. Cytoplasmic and nuclear expression levels are indicated as FPKM values. GAS6-AS1 exhibits variable intracellular distribution across different cancer types. Although computational prediction and transcriptomic analyses indicate differences in its predicted localization, experimental studies demonstrate that GAS6-AS1 may be predominantly localized in the cytoplasm, enriched in the nucleus or distributed between both compartments depending on the cellular and tumour context. These distinct localization patterns may contribute to the diverse molecular mechanisms of GAS6-AS1, including competitive endogenous RNA-mediated regulation, transcriptional modulation and interaction with RNA-binding proteins. CN RCI, cytoplasmic-to-nuclear relative concentration index; GAS6, growth arrest specific 6; AS1, antisense 1.

According to GLOBOCAN 2022, ~2.3 million new cases and 666,000 deaths from female BRCA occurred globally (22). Tumor metastasis and recurrence remain major challenges in BRCA management (26). Therefore, identifying molecular mechanisms underlying BRCA progression is essential for improving treatment strategies. Wu *et al* (27) investigated the role of GAS6-AS1 and its potential mechanisms in BRCA progression through functional experiments. Knockdown of GAS6-AS1 significantly reduced the proliferation and colony-forming capacity of BRCA cells. Additionally, GAS6-AS1 enhances the expression of SOX9 by isolating miR-215-5p as an endogenous RNA competitor. SOX9 is a transcription factor involved in stem cell maintenance, differentiation and tumor progression. The impact of GAS6-AS1 downregulation on BRCA malignant phenotypes can be mitigated by inhibiting miR-215-5p or restoring SOX9. These findings indicate that GAS6-AS1 promotes BRCA progression through the GAS6-AS1/miR-215-5p/SOX9 axis. Furthermore, this signaling pathway may contribute to tumor aggressiveness and metastasis. Therefore, GAS6-AS1 acts as a tumor-driving lncRNA in BRCA and regulates BRCA progression through the miR-215-5p/SOX9 axis. The GAS6-AS1/miR-215-5p/SOX9 axis represents a potentially effective target for cancer treatment and management.

GAS6-AS1 and hepatocellular carcinoma (HCC). HCC is one of the most common and aggressive malignant tumors in humans, with a high incidence rate (28). Chronic hepatitis virus infection, alcohol abuse, aflatoxin exposure and metabolic disorders are major risk factors for HCC development. Currently, surgical resection, radiofrequency ablation and liver transplantation are the primary treatment modalities for HCC (29). Despite significant improvements in diagnostic methods and therapeutic approaches for HCC, its clinical management remains suboptimal (30). A study reported that patients with HCC exhibiting high expression of GAS6-AS1 demonstrated significantly shorter overall survival compared to those with low GAS6-AS1 expression (31). Knocking down GAS6-AS1 *in vitro* inhibits HCC cell proliferation, colony formation, migration and invasion, promotes apoptosis *in vitro* and reduces tumor growth *in vivo*. These findings indicate that GAS6-AS1 plays a critical oncogenic role in HCC progression. GAS6-AS1 has been validated as a ceRNA for miR-585, increasing the expression of EIF5A2. EIF5A2 is known to promote tumor progression, metastasis and drug resistance in

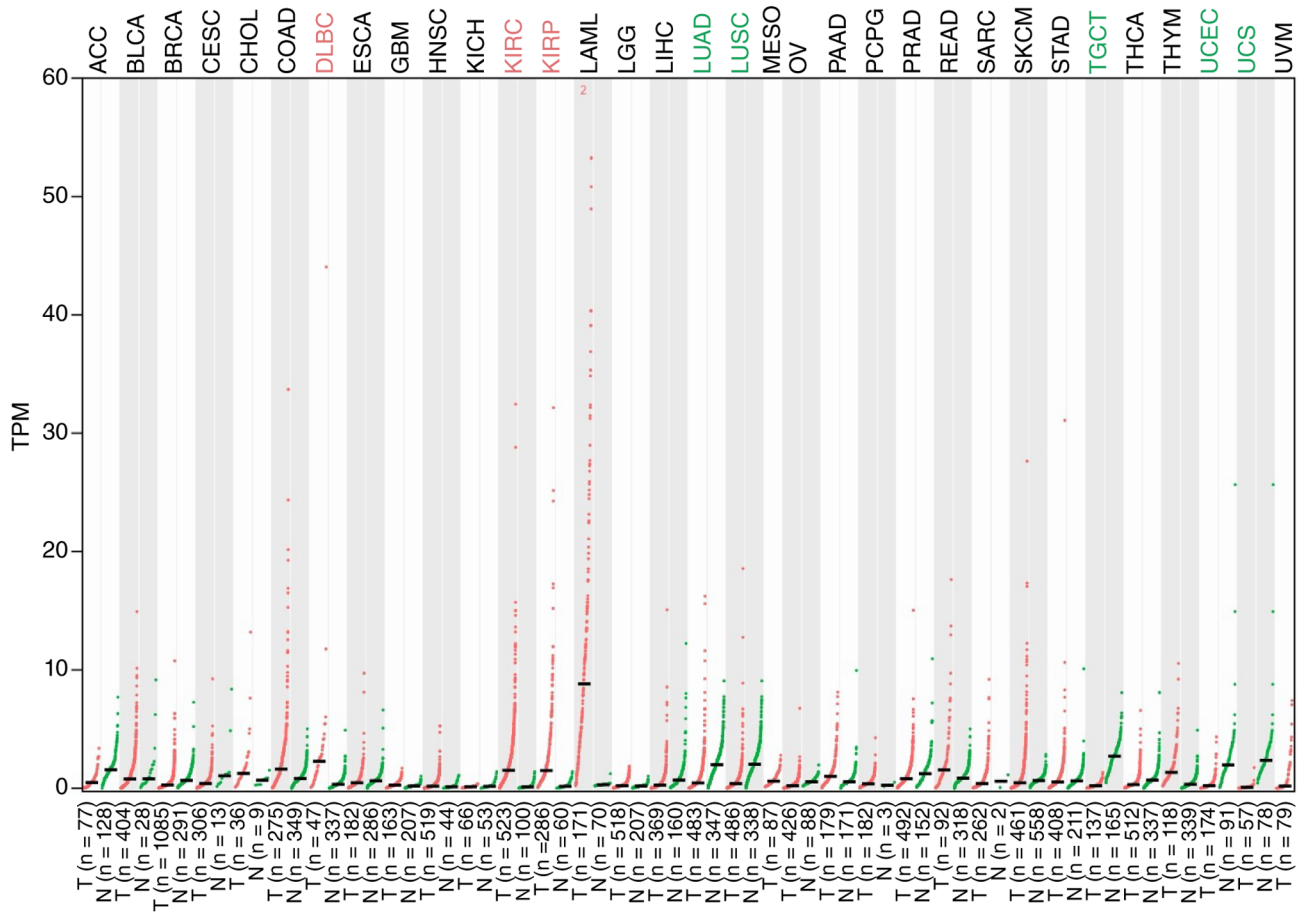

Figure 4. Expression profile of GAS6-AS1 across human cancer types. The expression levels of GAS6-AS1 in multiple tumor types and corresponding normal tissues were analyzed using the Gene Expression Profiling Interactive Analysis database. Log_2(fold change): 1; Q value: 0.01. GAS6-AS1 expression is presented as TPM, with comparisons between T and N tissues across different cancer types. The plot demonstrates the differential expression patterns of GAS6-AS1 among various malignancies, suggesting its potential involvement in tumor development and progression. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; N, normal tissue sample; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectal adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; T, tumour sample; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; TPM, transcripts per million; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

several cancers. Experiments have confirmed the correlation between GAS6-AS1, miR-585 and EIF5A2 in HCC cells (31). Therefore, the GAS6-AS1/miR-585/EIF5A2 pathway plays a crucial role in HCC progression and holds promise as a potential therapeutic target for HCC treatment.

GAS6-AS1 and AML. AML is a heterogeneous hematologic malignancy characterized by rapid cell proliferation, aggressive clinical course and poor prognosis (32). Although advances in chemotherapy and hematopoietic stem cell transplantation have improved survival in certain patients, relapse and treatment resistance remain major obstacles. Lei *et al* (33) found that GAS6-AS1 and TSPAN3 were overexpressed in pediatric patients with AML and leukemia cells, while miR-370-3p expression was downregulated. *In vitro*, GAS6-AS1 knockdown inhibited the viability, migration and invasion of AML cells. Additionally, GAS6-AS1 regulates the expression of miR-370-3p, with TSPAN3 identified as a target of miR-370-3p. Furthermore, overexpression of miR-370-3p suppresses the protein expression of TSPAN3. Experiments have demonstrated that inhibition of miR-370-3p or overexpression of TSPAN3 attenuates the inhibitory effect of GAS6-AS1 knockdown on AML cells. These findings indicate that GAS6-AS1 contributes to AML progression through the miR-370-3p/TSPAN3 axis. Therefore, GAS6-AS1 holds promise as a novel therapeutic target for pediatric AML.

GAS6-AS1 and ovarian cancer (OC). OC is one of the most lethal gynecological cancers, characterized by vague clinical symptoms and high rates of recurrence and mortality (34). Most patients with OC are diagnosed at advanced stages because early-stage disease often lacks obvious symptoms. Although diagnostic and therapeutic approaches for OC have improved, the prognosis remains poor (22). Currently, biomarkers for cancer diagnosis and treatment have garnered significant attention, but those for OC diagnosis or prognosis remain scarce and lack sufficient sensitivity and specificity (34). A study found that GAS6-AS1 is highly expressed in OC tissues and cells.

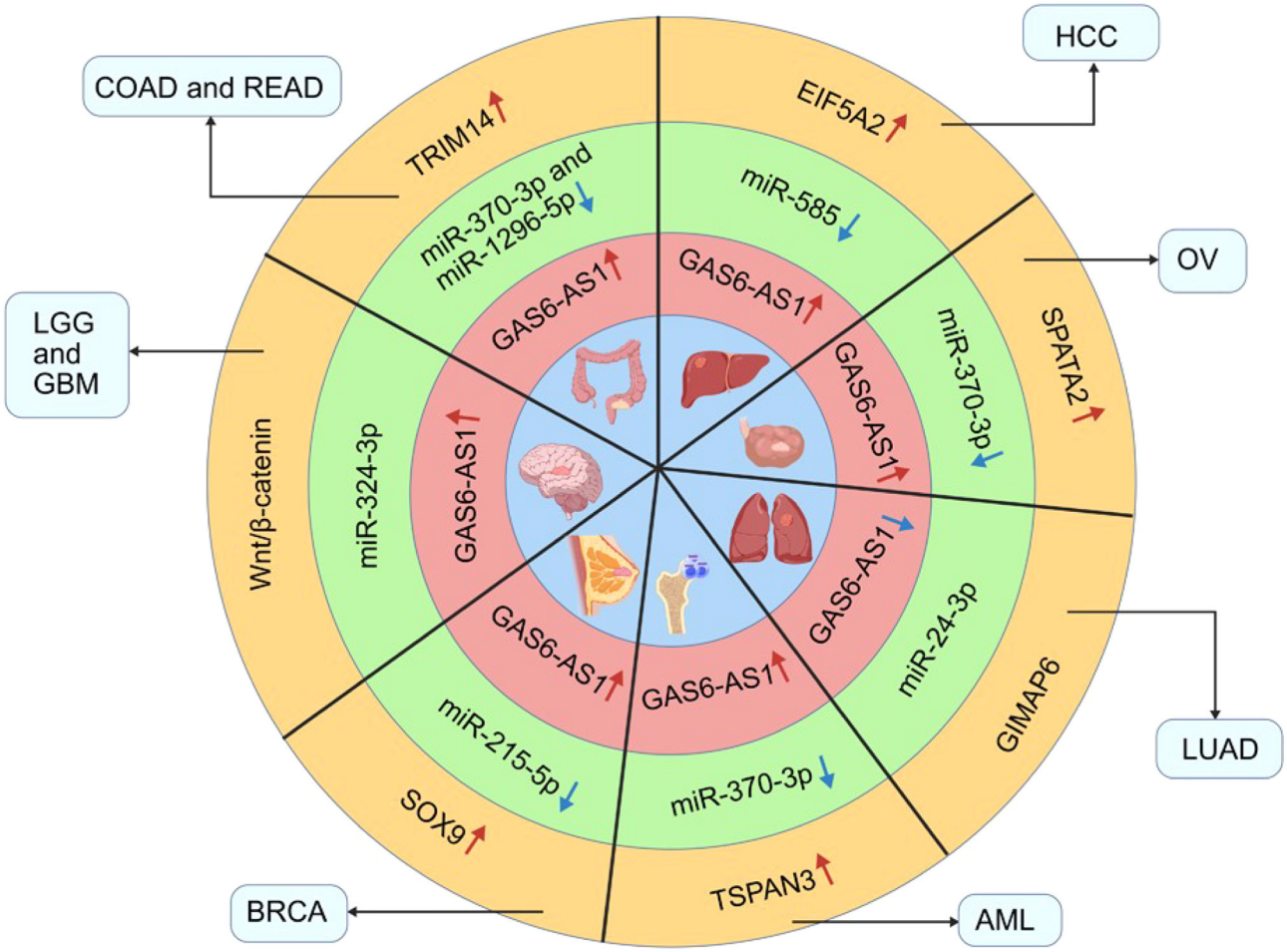

Figure 5. Molecular regulatory networks and biological functions of GAS6-AS1 in human cancers. Schematic illustration of the regulatory mechanisms and downstream targets of GAS6-AS1 across different cancer types. GAS6-AS1 functions as a competitive endogenous RNA by interacting with multiple miRNAs, including miR-370-3p, miR-1296-5p, miR-585, miR-215-5p, miR-324-3p and miR-24-3p, thereby regulating downstream target genes such as TRIM14, EIF5A2, SPATA2, SOX9, TSPAN3 and GIMAP6. GAS6-AS1 contributes to tumor progression through modulation of cancer-related pathways, including Wnt/β-catenin signaling, and affects malignant phenotypes such as cell proliferation, migration, invasion, epithelial–mesenchymal transition, apoptosis, metabolic reprogramming and therapeutic resistance. The specific GAS6-AS1 regulatory axes in COAD/READ, OV, HCC, BRCA, AML, LUAD and LGG/GBM are illustrated. Red arrows indicate upregulation or activation, whereas blue arrows indicate downregulation or inhibition. miRNA/miR, microRNA; COAD, colon adenocarcinoma; READ, rectal adenocarcinoma; OV, ovarian cancer; HCC, hepatocellular carcinoma; BRCA, breast cancer; AML, acute myeloid leukemia; LUAD, lung adenocarcinoma; LGG, lower-grade glioma; GBM, glioblastoma multiforme; TRIM14, tripartite motif-containing 14; SOX9, SRY-box transcription factor 9; EIF5A2, eukaryotic translation initiation factor 5A2; TSPAN3, tetraspanin 3; SPATA2, spermatogenesis associated 2; GIMAP6, GTPase immunity-associated protein 6.

Knockdown of GAS6-AS1 reduced the proliferation, invasion and metastasis capabilities of OC cells while promoting apoptosis (20). Additionally, knockdown of GAS6-AS1 also increased the expression of miR-370-3p in OC cells. Therefore, GAS6-AS1 knockdown may suppress SPATA2 expression by upregulating miR-370-3p, thereby inhibiting SKOV3 cell proliferation, migration, invasion and EMT while promoting apoptosis. However, these findings were based primarily on functional assays in a single ovarian cancer cell line (SKOV3) and lacked *in vivo* validation; therefore, further studies using additional ovarian cancer cell lines, animal models and clinical samples are required to determine the broader applicability of this mechanism across different OC subtypes.

GAS6-AS1 and glioma. Glioma is the most common primary malignant brain tumor, characterized by high incidence and recurrence rates (35). Due to the invasive growth pattern of glioma and the presence of the blood-brain barrier, effective treatment remains challenging. The prognosis of patients with high-grade glioma remains poor despite multimodal therapy. A study found that GAS6-AS1 is highly expressed in glioma tissues. GAS6-AS1 targets miR-324-3p to activate the Wnt/β-catenin pathway, thereby promoting T98G cell proliferation and invasion while reducing radiosensitivity (20,35). The Wnt/β-catenin pathway is an important signaling pathway involved in tumor progression, stemness maintenance and therapy resistance. By activating this pathway, GAS6-AS1 contributes to glioma malignancy and radioresistance. This mechanism may represent a potential new therapeutic strategy for glioma treatment. However, the mechanistic conclusions were mainly based on experiments performed in T98G cells and further validation in additional glioma cell lines and molecular subtypes is needed to establish the generalizability of these findings.

Notably, miR-370-3p emerges as a recurrent downstream regulatory node of GAS6-AS1 across different cancer types. GAS6-AS1 has been reported to sponge miR-370-3p in CRC,

Table II. CeRNA-dependent regulatory networks of GAS6-AS1 across human cancers.

Cancer type	Cell lines	Expression	Role	Target	Effects of GAS6-AS1	(Refs.)
Colorectal cancer	-	Up-regulated	Oncogene	ceRNA (miR-370-3p/miR-1296-5p → TRIM14); recruits FUS to stabilize TRIM14 mRNA	Promotes proliferation, migration, invasion and EMT; enhances tumor growth and metastasis	(5)
Lung adenocarcinoma	A549, H1299, PC9, H1975, HBE	Down-regulated	Tumor suppressor	ceRNA (miR-24-3p → GIMAP6)	Inhibits proliferation, migration and invasion; suppresses tumor progression	(21)
Breast cancer	MCF-7, MDA-MB231, SKBR3, MDAMB-468, MCF-10A	Up-regulated	Oncogene	GAS6-AS1/miR-215-5p/SOX9 axis (ceRNA mechanism)	Promotes proliferation and colony formation; facilitates tumor progression	(27)
Hepatocellular carcinoma	L-O2, Hep3B, Huh7, Bel7402	Up-regulated	Oncogene	GAS6-AS1/miR-585/EIF5A2 axis (ceRNA mechanism)	Promotes proliferation, migration and invasion; inhibits apoptosis; enhances tumor growth	(31)
Acute myeloid leukemia	-	Up-regulated	Oncogene	GAS6-AS1/miR-370-3p/TSPAN3 axis (ceRNA mechanism)	Promotes cell viability, migration and invasion	(33)
Ovarian cancer	-	Up-regulated	Oncogene	GAS6-AS1/miR-370-3p/SPATA2 axis (ceRNA mechanism)	Promotes proliferation, migration, invasion and EMT; inhibits apoptosis	(20)
Glioma	U87GR,U373GR	Up-regulated	Oncogene	miR-324-3p/Wnt/β-catenin pathway	Promotes proliferation and invasion; reduces radiosensitivity	(35)

The regulatory axes listed in this table represent experimentally validated ceRNA-dependent mechanisms of GAS6-AS1 across different human cancers. ceRNA, competitive endogenous RNA; GAS6-AS1, growth arrest-specific 6 antisense RNA 1; miR, microRNA; TRIM14, tripartite motif-containing 14; SOX9, SRY-box transcription factor 9; EIF5A2, eukaryotic translation initiation factor 5A2; TSPAN3, tetraspanin 3; SPATA2, spermatogenesis associated 2; GIMAP6, GTPase immunity-associated protein 6.

AML and OC, while regulating distinct downstream targets, including TRIM14, TSPAN3 and SPATA2, respectively. These findings suggest that GAS6-AS1 may utilize a shared miRNA node to control tumor-specific downstream effectors, highlighting the context-dependent and multi-layered nature of GAS6-AS1-mediated ceRNA regulation.

Direct protein-binding and transcriptional regulatory mechanisms of GAS6-AS1

GAS6-AS1/poly(rC)-binding protein 1 (PCBP1)/minichromosome maintenance complex component 3 (MCM3) axis in CRC chemoresistance. In recent years, lncRNAs have emerged as key regulators in various pathophysiological processes, including 5-fluorouracil (5-FU) resistance. Chemoresistance is a major factor limiting the effectiveness of cancer treatment and contributing to poor prognosis in patients with CRC. Zhu *et al* (8) confirmed through RNA-seq combined with weighted gene correlation network analysis that GAS6-AS1 is closely associated with tumor regression grade and can serve as a sensitive indicator for predicting prognosis in patients with CRC. *In vitro*, GAS6-AS1 increased the IC50 of 5-FU and enhanced cell proliferation, whereas *in vivo*, it reduced the therapeutic efficacy of 5-FU and promoted tumor growth. In CRC cells, GAS6-AS1 directly interacts with PCBP1 and recruits PCBP1 to MCM3 mRNA, thereby enhancing MCM3 mRNA stability and consequently increasing MCM3 expression. This GAS6-AS1/PCBP1/MCM3 regulatory mechanism contributes to 5-FU resistance, cell proliferation and G1/S cell-cycle progression in CRC. These findings suggest that GAS6-AS1 promotes tumor progression not only through ceRNA mechanisms but also through direct interactions with RNA-binding proteins involved in DNA replication and cell cycle regulation. Therefore, GAS6-AS1 can serve as a reliable biomarker and potential therapeutic target for combination therapy in CRC.

GAS6-AS1 regulation of GAS6/AXL signaling in gastric cancer (GC). GC remains a major global health burden, ranking fifth worldwide in both cancer incidence and cancer-related mortality according to GLOBOCAN 2022 (22), with its incidence rapidly increasing. Environmental factors, *Helicobacter pylori* infection, dietary habits and genetic susceptibility all contribute to GC development. Like other human cancers, GC is a complex disease involving biological processes and genetic alterations (36). Zhang *et al* (4) found that GAS6-AS1 is upregulated in GC tissues and is associated with advanced GC. GAS6-AS1 promotes cell proliferation, migration and invasion *in vitro* by facilitating entry into S phase, and enhances the growth of xenograft tumors *in vivo*. Importantly, GAS6-AS1 has been reported to form an RNA-RNA duplex with the GAS6 transcript, thereby increasing GAS6 expression and subsequently activating downstream AXL signaling. This interaction is consistent with a post-transcriptional regulatory mechanism; however, whether the RNA duplex primarily enhances GAS6 mRNA stability or translational efficiency has not yet been fully resolved. The AXL signaling pathway plays an important role in tumor proliferation, invasion, EMT, angiogenesis, immune escape and therapeutic resistance (4). This finding establishes the first link between GAS6-AS1 expression and GC tumorigenesis and progression, suggesting that GAS6-AS1 may serve as a novel diagnostic marker and therapeutic biomarker for GC.

GAS6-AS1/E2F1/GLUT1 axis in LUAD. The proliferation and growth of solid tumors lead to insufficient energy supply. Glucose serves as the primary energy source supporting tumor growth and also provides a carbon source for biosynthetic reactions (37). Tumor cells often undergo metabolic reprogramming characterized by enhanced glycolysis, also known as the Warburg effect. Luo *et al* (6) found that GAS6-AS1 is downregulated in LUAD, and its overexpression inhibits the progression of LUAD both *in vivo* and *in vitro*. Metabolic experiments revealed that GAS6-AS1 suppresses glucose metabolic reprogramming, and it was found to inhibit the expression of GLUT1. Further studies revealed that GAS6-AS1 directly interacts with the transcription factor E2F1, thereby inhibiting E2F1-mediated GLUT1 transcription. Since GLUT1 is essential for glucose uptake in tumor cells, suppression of GLUT1 expression can significantly inhibit tumor growth and metabolic activity. The study results identify GAS6-AS1 as a novel tumor suppressor in LUAD and reveal its potential molecular mechanism in glucose metabolism reprogramming. GAS6-AS1 may therefore serve as a prognostic biomarker and therapeutic target for LUAD. Taken together, current evidence suggests that GAS6-AS1 exerts tumor-suppressive effects in LUAD through at least two complementary regulatory mechanisms. On the one hand, GAS6-AS1 functions as a ceRNA for miR-24-3p to increase GIMAP6 expression and suppress malignant phenotypes; on the other hand, it directly interacts with E2F1 to repress E2F1-mediated GLUT1 transcription, thereby restricting glucose metabolic reprogramming. These findings highlight the mechanistic versatility of GAS6-AS1 in LUAD and suggest that its tumor-suppressive activity involves both post-transcriptional ceRNA regulation and transcription factor-mediated metabolic control.

GAS6-AS1/Y-box binding protein 1 (YBX1)/MYC axis in AML. A study analyzed AML microarray chips and public datasets, established functional leukemic cell models and validated their leukemic phenotypes via *in vitro* and *in vivo* experiments (7). Results demonstrated that GAS6-AS1 is overexpressed in AML, and its aberrant function leads to a more aggressive leukemic phenotype and poorer survival outcomes. Furthermore, downregulation of GAS6-AS1 inhibits leukemia progression *in vivo*. Mechanistically, GAS6-AS1 directly binds to YBX1, promoting its interaction with MYC, leading to MYC transactivation and upregulation of MYC target genes implicated in leukemia progression, such as IL-1 receptor type 1 and RAB27B, member RAS oncogene family. MYC is one of the most important oncogenic transcription factors in human cancers and regulates genes associated with proliferation, metabolism, apoptosis and stemness. Therefore, GAS6-AS1-mediated activation of MYC signaling may significantly contribute to leukemia progression. These findings further expand the understanding of GAS6-AS1-mediated oncogenic mechanisms and suggest that targeting the GAS6-AS1/YBX1/MYC axis may provide a novel therapeutic strategy for AML. Taken together, current evidence indicates that GAS6-AS1 promotes AML progression through at least two distinct regulatory mechanisms. In addition to the GAS6-AS1/miR-370-3p/TSPAN3 ceRNA axis described above, GAS6-AS1 is predominantly localized in

the nucleus of AML cells and directly interacts with YBX1 to enhance its association with MYC, thereby promoting MYC transactivation and the expression of downstream oncogenes. These findings highlight the mechanistic versatility of GAS6-AS1 in AML, involving both ceRNA-mediated post-transcriptional regulation and nuclear protein-mediated transcriptional control.

4. Clinical significance and prognostic value of lncRNA GAS6-AS1 in human cancers

Beyond its mechanistic roles, accumulating clinical and bioinformatic evidence suggests that GAS6-AS1 expression is associated with tumor progression, clinicopathological characteristics and patient prognosis in multiple cancer types. These findings support its potential value as a diagnostic and prognostic biomarker, although its clinical significance appears to be tumor context-dependent. The available clinical and prognostic evidence regarding GAS6-AS1 is summarized in Table III.

GAS6-AS1 and CRC. The state of cellular proliferation during tumor progression involves corresponding alterations in cellular metabolism (38). Changes in the activity and levels of metabolic products may effectively promote tumor growth (39). Metabolism-related lncRNAs can aid in detecting tumorigenesis and progression in patients with CRC. Lu *et al* (40) obtained transcriptomic data of patients with CRC from public databases and identified lncRNAs with significant clinical value related to metabolism-associated genes, among which GAS6-AS1 was included. They constructed a novel model integrating metabolic risk scores and clinical parameters to predict prognosis in patients with CRC. These findings suggest that GAS6-AS1 may participate in metabolic regulation during CRC progression and could contribute to prognostic prediction models.

GAS6-AS1 and LUAD. Chen *et al* (41) constructed an autophagy-related mRNA-lncRNA expression network using Pearson correlation coefficients. They evaluated the prognostic value of autophagy-related lncRNAs through univariate and multivariate Cox proportional hazards analyses, ultimately identifying a survival model composed of 11 autophagy-related lncRNAs, including GAS6-AS1. The risk score model constructed using 11 autophagy-related lncRNAs demonstrated the highest diagnostic performance (area under curve=0.809) compared to other clinical feature models. Therefore, the risk score model comprising 11 autophagy-related lncRNAs holds significant predictive value for the prognosis of LUAD and may serve as a potential therapeutic target for autophagy-related clinical interventions. Of note, Han *et al* (42) reported an inverse correlation between GAS6-AS1 and GAS6 mRNA expression in NSCLC, which contrasts with the positive regulation of GAS6 by GAS6-AS1 through RNA-RNA duplex formation reported in GC (4). Notably, the NSCLC study demonstrated a correlation but did not establish a direct regulatory mechanism. These findings suggest that the relationship between GAS6-AS1 and its cognate sense gene GAS6 may be highly context dependent and could vary according to tumor type or cellular environment. Further mechanistic studies are required to clarify the basis of these contrasting regulatory patterns.

GAS6-AS1 and BRCA. Previous studies have reported inconsistent expression patterns of GAS6-AS1 in BRCA. Wu *et al* (27) observed increased GAS6-AS1 expression in BRCA tissues and demonstrated its oncogenic function through the miR-215-5p/SOX9 axis. By contrast, Lavasani *et al* (43) reported significantly reduced GAS6-AS1 expression in breast tumor tissues compared with paired non-cancerous tissues and identified an association between GAS6-AS1 expression and progesterone receptor status. These apparently conflicting findings may reflect differences in patient cohorts, molecular or hormone-receptor characteristics, sample composition and experimental approaches. However, the available evidence does not yet establish whether specific molecular subtypes of BRCA account for this discrepancy. Further studies using larger, molecularly stratified cohorts are therefore required to clarify the context-dependent expression and biological role of GAS6-AS1 in BRCA.

GAS6-AS1 and renal cell carcinoma (RCC). Chen *et al* (41) obtained cancer-associated lncRNAs by downloading RNA sequencing profiles and clinical characteristics of kidney renal papillary cell carcinoma cases from databases. They further analyzed differentially expressed cancer-associated lncRNAs in papillary renal cell carcinoma. A total of 10 lncRNAs (including GAS6-AS1) were identified as independently associated with prognosis in papillary renal cell carcinoma. Yang *et al* (44) downloaded lncRNA expression data and corresponding clinical data for patients with papillary renal cell carcinoma from databases. A total of 17 lncRNAs were identified as key lncRNAs (including GAS6-AS1). This study may lay the foundation for further investigation into the potential mechanisms underlying the occurrence and development of papillary renal cell carcinoma. Lan *et al* (45) employed multivariate Cox regression analysis to demonstrate that a prognostic index comprising seven lncRNAs (including GAS6-AS1) can accurately predict the progression and outcomes of renal papillary cell carcinoma. He *et al* (46) constructed a ceRNA network and established a prognostic signature using a combination of univariate Cox regression and stepwise regression. The predictive performance was validated using receiver operating characteristic curves. The eight identified lncRNAs, among which was GAS6-AS1, may serve as novel and crucial prognostic factors involved in the pathogenesis of renal papillary cell carcinoma. Therefore, GAS6-AS1 holds potential as a valuable prognostic indicator for RCC.

GAS6-AS1 and esophageal squamous cell carcinoma (ESCC). Esophageal cancer is a common malignant tumor, with ESCC being the predominant histological subtype (47). Lymph node metastasis is an important factor associated with poor prognosis in ESCC. Xie *et al* (48) identified GAS6-AS1 as an independent risk factor for lymph node metastasis and a potential biomarker for disease prediction. GAS6-AS1 was highly expressed in ESCC tissues, particularly in cases with lymph node metastasis. Functional studies showed that GAS6-AS1 knockdown suppressed cell growth and metastatic potential,

Table III. Clinical significance of GAS6-AS1 in human cancers.

Cancer type	Numbers of clinical samples	Expression status in cancers	Diagnostic value	Clinicopathological correlation	Prognostic significance	(Refs.)
Colorectal cancer	-	Up-regulated	Potential diagnostic/ therapeutic biomarker	Associated with tumor progression, metastasis and EMT	High GAS6-AS1 predicts poor prognosis	(5)
LUAD	80 pairs of LUAD tissues and ANCTs	Down-regulated	Potential diagnostic biomarker	Associated with tumor progression	Low GAS6-AS1 predicts poor OS	(21)
NSCLC	50 patients with primary NSCLC and ANCTs	Down-regulated	Potential diagnostic biomarker	Associated with tumor progression	Low GAS6-AS1 predicts poor OS	(21)
BRCA	60 pairs of BRCA tissues and ANCTs	Up-regulated	Potential therapeutic target	Associated with malignant progression	Potential prognostic biomarker	(43)
HCC	47 pairs of fresh HCC tissue samples and ANCTs	Up-regulated	Potential therapeutic target	Associated with aggressive tumor progression	High GAS6-AS1 predicts shorter OS	(31)
Acute myeloid leukemia	-	Up-regulated	Potential therapeutic target	Associated with leukemic progression	Potential prognostic biomarker	(33)
GC	55 pairs of GC tissues and ANCTs	Up-regulated	Potential diagnostic/ therapeutic biomarker	Associated with tumor progression	High GAS6-AS1 predicts poor prognosis	(4)
Ovarian cancer	-	Up-regulated	Potential diagnostic/ therapeutic biomarker	Associated with malignant progression, metastasis and EMT	Potential prognostic biomarker	(20)
Glioma	-	Up-regulated	Potential therapeutic target	Associated with tumor progression and radioresistance	Potential prognostic biomarker	(35)
KIRP	TCGA analysis: 321 KIRP tissues and 32 ANCTs	Up-regulated	Potential diagnostic biomarker	-	High GAS6-AS1 predicts poor prognosis	(46)

GAS6-AS1, growth arrest-specific 6 antisense RNA 1; OS, overall survival; EMT, epithelial-mesenchymal transition; HCC, hepatocellular carcinoma; ANCTs, adjacent non-cancerous tissues; BRCA, breast cancer; KIRP, kidney renal papillary cell carcinoma; NSCLC, non-small cell lung cancer; LUAD, lung adenocarcinoma; GC, gastric cancer; TCGA, The Cancer Genome Atlas.

inhibited tumor growth *in vivo*, induced G1-phase cell-cycle arrest, reduced the S-phase population and increased apoptosis. These findings suggest that GAS6-AS1 contributes to tumor cell survival and metastatic progression in ESCC. However, the specific downstream molecular intermediates and signaling pathways linking GAS6-AS1 to cell-cycle regulation and apoptosis were not identified in this study and remain to be elucidated.

Collectively, these bioinformatic and database-mining studies support GAS6-AS1 as a promising prognostic biomarker across several cancer types and suggest its potential involvement in diverse biological processes, including autophagy and metabolic regulation. However, most of these associations are derived from computational analyses and prognostic modeling and therefore do not establish direct biological causality. Further validation using independent clinical cohorts and functional experiments is required to confirm the physiological roles of GAS6-AS1 in these predicted regulatory networks.

5. Conclusions and future perspectives

LncRNAs are key regulators in tumorigenesis and tumor progression. Research on lncRNAs in tumors is expanding and their impact on cancer progression is gaining increasing attention. Current research indicates that GAS6-AS1 is an oncogenic lncRNA that is highly expressed in multiple cancers and serves as a potential prognostic biomarker for various cancers. However, its biological role may differ depending on tumor type and cellular context, as demonstrated by its tumor-suppressive role in LUAD. Accumulating evidence indicates that GAS6-AS1 participates in multiple aspects of tumor biology, including proliferation, invasion, migration, EMT, glycolysis, apoptosis, therapeutic resistance and metabolic reprogramming. GAS6-AS1 exerts these functions through diverse molecular mechanisms, including ceRNA-mediated miRNA regulation, modulation of signaling pathways, interaction with transcription factors and binding to RNA-binding proteins.

Emerging evidence also suggests a potential relationship between GAS6-AS1 and the tumor immune microenvironment. GAS6/AXL signaling has been reported to contribute to immunosuppressive tumor conditions by regulating tumor-associated macrophages and T-cell responses, and inhibition of this pathway may enhance the efficacy of immune checkpoint blockade (49,50). Given that GAS6-AS1 can regulate GAS6 expression and AXL signaling, GAS6-AS1 may potentially participate in tumor immune regulation through this axis. However, direct evidence linking GAS6-AS1 to immune-cell infiltration, immune evasion or immunotherapy response remains limited and warrants further investigation.

Recent studies further highlight that cancer-associated lncRNAs function within complex and multilayered regulatory networks rather than through isolated linear pathways. Patient-specific analyses of lncRNA-miRNA-mRNA networks have revealed substantial interpatient heterogeneity and identified regulatory RNA triplets with potential prognostic relevance across multiple cancer types (51). Furthermore, genome-scale functional screening in melanoma identified several lncRNAs associated with BRAF inhibitor resistance and linked them to an integrated lncRNA-miRNA-mRNA regulatory network (52). Similar network-based studies in HPV16-positive oropharyngeal cancer and LUAD have further demonstrated that lncRNAs participate in extensive interactions with miRNAs, mRNAs and protein-coding genes that collectively influence tumor progression (53,54). Importantly, lncRNA-mediated regulation is not restricted to ceRNA crosstalk; recent mechanistic evidence has shown that lncRNAs can interact directly with chromatin-associated proteins to modulate downstream gene transcription, as exemplified by the maternally expressed 3/CCCTC-binding factor/C-X-C motif chemokine receptor 4 regulatory axis in BRCA (55). These recent advances suggest that future studies of GAS6-AS1 should move beyond individual regulatory axes and integrate multi-omics profiling, RNA-protein interaction analysis and patient-specific network modeling to define context-dependent regulatory modules and identify clinically actionable vulnerabilities.

Furthermore, its inhibitory effects both *in vivo* and *in vitro* significantly suppress the proliferation, migration and invasion of various cancer cells, indicating that GAS6-AS1 represents a potential therapeutic target for cancer treatment. Certain researchers believe that GAS6-AS1 could serve as a biomarker for cancer diagnosis; however, the evidence in this area remains somewhat limited and warrants further investigation. At present, several limitations remain in GAS6-AS1 research. First, most studies are still limited to cell experiments and animal models, and large-scale clinical validation studies are lacking. Second, the precise upstream regulatory mechanisms controlling GAS6-AS1 expression remain incompletely understood. Third, the clinical translation of GAS6-AS1-targeted strategies still faces several challenges, including inefficient and tissue-specific delivery of RNA therapeutics, potential off-target effects, limited stability and possible toxicity or immune-related adverse effects. Therefore, the long-term safety, delivery efficiency, specificity and therapeutic feasibility of targeting GAS6-AS1 require systematic evaluation in appropriate preclinical and clinical models. In the future, more studies are needed to elucidate the comprehensive molecular network regulated by GAS6-AS1. Integration of transcriptomics, proteomics and metabolomics may help uncover novel functions and interacting partners of GAS6-AS1. Furthermore, advances in RNA-targeted therapeutics, including antisense oligonucleotides, small inhibitory RNA and CRISPR-based technologies, together with the development of more efficient and tumor-selective delivery systems, may facilitate the future development of GAS6-AS1-targeted therapies. An important unresolved question is why GAS6-AS1 exhibits opposite functions across different tumor contexts. Future multi-omics studies should investigate whether tissue-specific epigenetic states, transcriptional regulation and distinct RNA/protein interactions underlie this functional switch. In addition, given the involvement of GAS6-AS1 in E2F1/GLUT1-mediated glucose metabolic reprogramming, integration of metabolomics and metabolic flux analyses with transcriptomic and proteomic profiling will be important for defining its metabolic functions and validating the corresponding regulatory models. In summary, this review highlights the scope for future research

on the role of GAS6-AS1 in various cancers, expands the understanding of cancer pathogenesis and provides new insights for developing novel biomarkers and personalized cancer therapies.

Acknowledgements

The figures were created with Adobe Illustrator CC 2020 (version 24.0.1; Adobe Inc.) and draw.io.

Funding

This study was supported by the National Natural Science Foundation of China (grant no. 82160516), Yunnan Provincial Fundamental Research Projects (grant nos. 202201AT070004 and 202301AT070023), Yunnan Provincial Ten Thousand Talent Projects (grant no. 2019), Yunnan Provincial Local University Joint Projects (grant no. 202401BA070001-093), Scientific Research Fund of Yunnan Provincial Department of Education (grant nos. 2024J0836 and 2026Y1198), the Dali City Science and Technology Planning Projects (grant no. 2021KBG032), Open Project of Yunnan Provincial Key Laboratory of Entomological Biopharmaceutical R&D (grant nos. AG202203 and AP2022006), Project of Yunnan Key Laboratory of Screening and Research on Anti-pathogenic Plant Resources from Western Yunnan (grant no. 202549CE340077) and the Xingguo Liu Expert Workstation of Dali Bai Autonomous Prefecture (grant no. 202402).

Availability of data and materials

Not applicable.

Authors' contributions

ZL contributed to writing-original draft, visualization, validation and conceptualization. WH was involved in writing-original draft, visualization, validation and conceptualization. JH prepared the original draft and performed visualization and validation. LZ, FH and ZL were involved in visualization, literature search and selection, and data extraction. JL provided project administration, methodology, literature analysis and funding acquisition. WX was involved in writing-review and editing, validation, software, resources, project administration and funding acquisition. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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