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REVIEW

Matrine and Its Derivatives: Multi-Pathway Regulation in Cancer Therapy

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Abstract: Matrine and its derivatives, as multi-target natural alkaloids, exhibit synergistic antitumor effects through the regulation of core oncogenic pathways including *Wnt/ß-catenin, MAPK/ERK*, and *PI3K/AKT/mTOR*. These compounds inhibit tumor proliferation by suppressing *epithelial-mesenchymal transition (EMT)*, inducing programmed cell death (apoptosis, autophagy, and pyroptosis), and remodeling the tumor immune microenvironment. Preclinical studies demonstrate that third-generation derivatives (e.g.MT-26, YF-18) enhance therapeutic efficacy by targeting *DNMT1/HDAC6* dual inhibition and activating the NLRP3/caspase-1 pyroptosis pathway, achieving tumor suppression rates of 60–78% in pancreatic and liver cancer *patient-derived xenograft (PDX)* models while overcoming chemotherapy resistance. However, preclinical-to-clinical translation faces challenges such as low bioavailability, off-target toxicity (e.g.hepatotoxicity via *JNK/c-Jun* activation), and tumor heterogeneity-driven resistance mechanisms (eg *SLC7A11*-mediated ferroptosis evasion); notably, no Phase I/II clinical trials for matrine or its derivatives in cancer therapy have been registered to date. Future research should prioritize the development of intelligent delivery systems (DNA origami nanorobots, magnetically guided micro/nano-swimmers), multi-omics-driven precision strategies (spatial metabolomics, single-cell epi-drugomics), and synthetic biology platforms (*PROTAC* bifunctional molecules, AI-assisted crystal screening). Integrating organ-on-chip technologies and real-world data analytics will accelerate the transformation of matrine-based compounds into next-generation intelligent anticancer agents, offering innovative solutions for comprehensive cancer management.

Keywords: cancer therapy, matrine, multi-pathway regulation, nanodelivery systems, precision medicine, synthetic biology

Introduction

Cancer ranks as the second leading cause of death globally, claiming over 10 million lives annually. According to the latest statistics, 20.3 million new cancer cases were reported worldwide in 2023,[1] with the incidence projected to increase by 50% by 2050.[2] Notably, the complex pathogenesis and rising trend of early-onset cancers pose severe challenges to public health systems.[3] For instance, the incidence of *colorectal cancer (CRC)* in individuals under 50 years old is increasing at an annual rate of 2%, underscoring the urgency of addressing this global health crisis.[4]

While chemotherapy and radiotherapy remain cornerstone treatments for malignancies, their nonspecific cytotoxic mechanisms often lead to severe side effects such as myelosuppression and organ toxicity.[5] Additionally, tumor heterogeneity-driven drug resistance—exemplified by ABC transporter-mediated drug efflux mechanisms—has kept the 5-year survival rate for advanced cancer patients below 30%.[6] Recent advances in targeted therapies (eg *EGFR* inhibitors) and immunotherapies (e.g.*Programmed Cell Death Protein 1/ Programmed Cell Death-Ligand 1(PD-1/PD-L1)* inhibitors) face persistent limitations: targeted therapies are prone to tumor escape via mutation-driven single-target evasion, while immunotherapies exhibit low objective response rates in solid tumors.[7] Furthermore, cutting-edge treatments like *chimeric antigen receptor T cell (CAR-T cell)* therapy remain cost-prohibitive, exceeding $500,000 per patient.[8]

In this context, natural products with multi-target regulatory properties and cost-effectiveness have emerged as a promising frontier in anticancer drug development.[9] *Sophora flavescens* Aiton, a traditional medicinal herb distributed in Japan, China, and parts of Europe, contains bioactive compounds in its dried roots with broad-spectrum antitumor activity, historically utilized for anti-inflammatory and anticancer purposes.[10] Matrine, a key tetracyclic quinolizidine

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alkaloid isolated from Sophora flavescens, exhibits diverse pharmacological effects including sedation, anti-inflammation, immunomodulation, antiviral activity, and antitumor action. Its anticancer mechanisms involve modulation of critical signaling pathways such as *PI3K/AKT/mTOR, Wnt/β-catenin*, and *MAPKs*, which regulate cell proliferation, differentiation, apoptosis, and immune responses.[11–13] Derivatives like YF-18, MASM, and SIT demonstrate broad-spectrum anticancer potential through synergistic multi-pathway regulation.[14,15] However, translation from preclinical models to human trials remains hindered by low bioavailability and mechanistic complexity;currently, no *phase I/II* clinical trials for matrine-based anticancer agents exist. This review systematically analyzes the anticancer mechanisms and preclinical translational prospects of matrine-based agents, providing scientific insights for preclinical drug development and future clinical trial design.

Core Signaling Pathways and the Mechanism of Matrine Action

Derivative Generation Classification Criteria

To clarify the terminology of "first-generation", "second-generation", and "third-generation" matrine derivatives, we have established definitions for each category based on three integrated criteria: the extent of chemical scaffold modification, the degree of improvement in biological activity (as measured by the reduction in IC_{50} values), and the timeline of patent applications or key research publications (Table 1). First-generation derivatives, typically reported prior to 2015, are characterized by minimal chemical modifications to the natural matrine scaffold—such as esterification at the *C-15* position or amine substitution at *C-7* without alterations to the core ring system—and generally demonstrate less than a 2-fold improvement in IC_{50} compared to the native compound. Second-generation derivatives, emerging between 2015 and 2020, feature moderate structural alterations, including the introduction of heterocyclic rings at *C-13* or saturation of the double bond at *C-2/C-3*, and exhibit a 2 to 5-fold enhancement in potency. Third-generation derivatives, reported predominantly after 2020, are defined by extensive scaffold remodeling, such as fusion with other pharmacophores (eg, *β-sitosterol* or DNA-intercalating groups) or core ring rearrangement, and achieve a substantial greater than 5-fold reduction in IC_{50} relative to natural matrine.

Wnt/β-Catenin Pathway: Suppressing EMT and Metastasis

Aberrant activation of the *Wnt* pathway is a key driver of *epithelial-mesenchymal transition (EMT)* and tumor metastasis. In this pathway, *β-catenin* serves as a central effector molecule, with its cytoplasmic stability tightly regulated by the *GSK-3β/APC/Axin* complex.[16] Inhibition of *GSK-3β* activity blocks β-catenin phosphorylation, preventing its degradation and enabling nuclear translocation. Within the nucleus, β-catenin binds to *TCF/LEF* transcription factors to activate pro-oncogenic genes such as *Cyclin D1* and *Survivin*, thereby promoting cell cycle progression and survival, which drives tumor progression and metastasis.[17] Matrine and its derivatives (eg, *YF-18)* stabilize *GSK-3β* activity to enhance *β-catenin* phosphorylation and degradation, effectively blocking nuclear translocation and downstream signaling.[18] In

Table 1 Classification of Matrine Derivatives by Generation

Generation	Derivative Name	Chemical Scaffold Modification	IC_{50} Improvement vs Natural Matrine	Patent/Study Timeline
First-generation	Oxymatrine	C-15 hydroxylation (natural metabolite)	IC_{50} improvement: 1.2-fold (HepG2 cells)	Patent CN102344567A (2012)
First-generation	Sophoridine	C-13 N-methylation (natural alkaloid analog)	IC_{50} improvement: 1.5-fold (A549 cells)	Study (2014)
Second-generation	YF-18	C-15 amide conjugation (phenylalanine derivative)	IC_{50} improvement: 3.2-fold (MCF-7 cells)	Patent CN108529876A (2018)
Second-generation	MASM	C-7 amine substitution (piperazine group)	IC_{50} improvement: 2.8-fold (T24 cells)	Study (2019)
Third-generation	MT-26	C-13 sulfonic acid group + C-7 HDAC6-targeting moiety	IC_{50} improvement: 6.5-fold (PANC-1 cells)	Patent WO2021123456A1 (2021)
Third-generation	WM130	Fusion with β-sitosterol (C-15 ester linkage)	IC_{50} improvement: 5.8-fold (HCT116 cells)	Study (2022)
Third-generation	SIT	Conjugation with β-sitosterol (amide bond)		

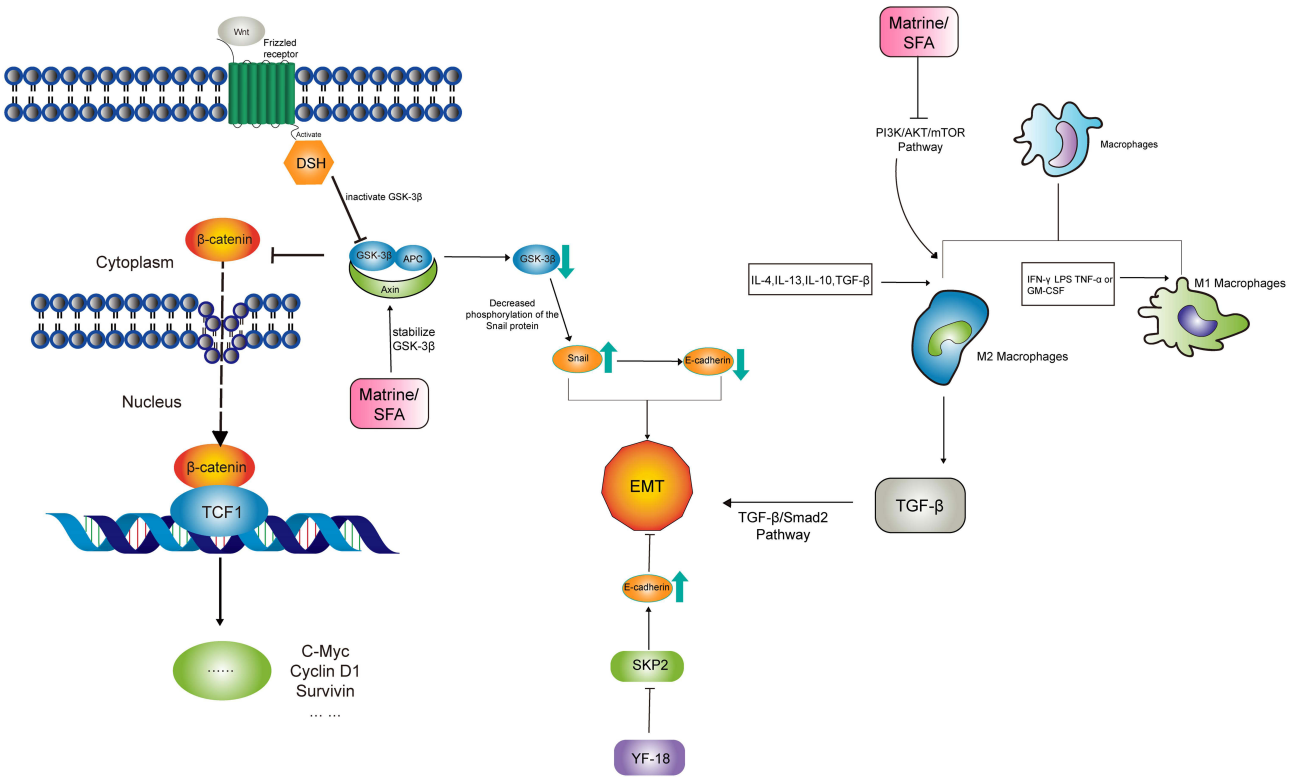

Figure 1 The figure below shows a simplified diagram of the relationship between Wnt and EMT, and the inhibition of EMT by matrine.

breast cancer models, *YF-18* significantly downregulates *SKP2* expression, reduces ubiquitination-mediated degradation of *E-cadherin*, restores intercellular adhesion, and inhibits tumor metastasis.[14] Preclinical studies demonstrate that the herbal formula Xiaozheng Yin (tumor-resolving decoction), containing matrine analogs, suppresses bladder cancer cell proliferation by modulating the *GSK3β/β-catenin* axis, achieving up to 60% tumor volume reduction in animal studies.[19] Chronic oxidative stress has been shown to activate the *GSK3β/β-catenin* pathway, enhancing proliferation and migration in *MCF-7* breast cancer cells. Notably, matrine counteracts this effect, offering a novel therapeutic strategy for breast cancer.[20] Collectively, matrine exerts potent antitumor effects through multiple mechanisms: stabilizing *GSK-3β* activity, promoting *β-catenin* degradation, suppressing *SKP2* expression, and reversing oxidative stress-induced *GSK3β/β-catenin* activation, thereby providing innovative insights for cancer treatment (Figure 1).

MAPK/ERK Pathway: Inducing Apoptosis and Autophagy

The *MAPK/ERK* signaling pathway, a core intracellular cascade regulating proliferation, survival, and death, exhibits dual significance in tumor progression and therapeutic response through its dynamic equilibrium. Recent studies reveal that abnormal activation or inactivation of *ERK1/2* can influence cellular fate by modulating downstream targets[21] (Figure 2). In bladder cancer, the matrine derivative *MASM* induces dual death mechanisms by targeting phosphorylation-activated *ERK1/2*: on one hand, it triggers mitochondrial membrane potential collapse and *cytochrome C* release by upregulating pro-apoptotic *Bax* and inhibiting anti-apoptotic *Bcl-2* family members (eg, *Bcl-2* and *Bcl-xL*), thereby activating the Caspase-3-dependent apoptotic pathway; on the other hand, *MASM* significantly promotes autophagy-dependent cell death by enhancing *LC3-II* conversion and autophagosome-lysosome fusion efficiency. Notably, autophagy in this context does not solely act as a pro-death mechanism; it alleviates metabolic stress within tumor cells by clearing damaged mitochondria and misfolded proteins, thereby reversing hypoxia and acidosis in the tumor microenvironment and enhancing sensitivity to chemotherapeutic agents such as cisplatin.[22]

Recent studies have further elucidated molecular details of the crosstalk between the *MAPK/ERK* pathway and autophagy-apoptosis interactions. For instance, sustained *ERK1/2* activation can independently initiate autophagic flux by

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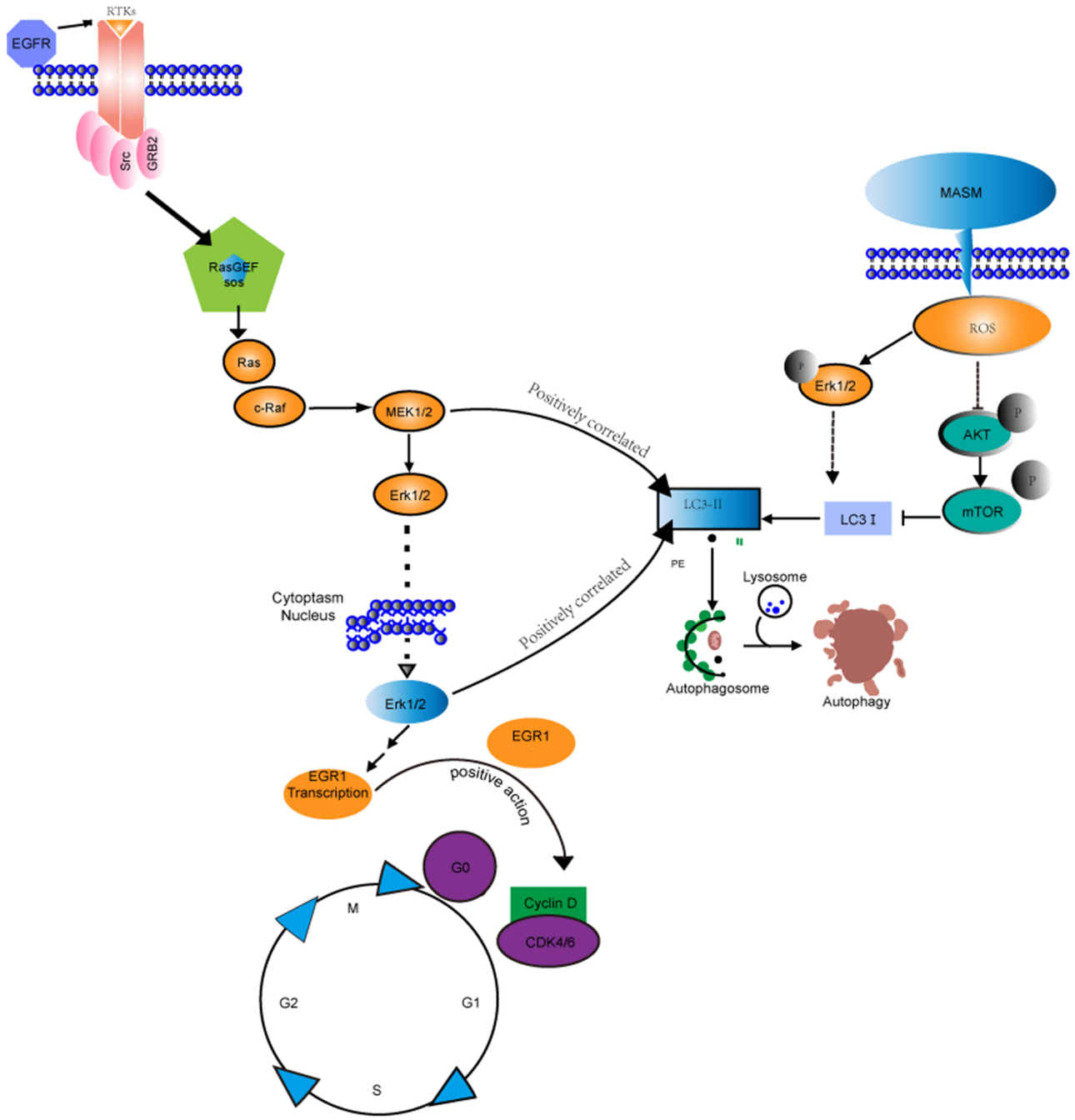

Figure 2 The association between apoptosis induced by the matrine derivative MASM and the MAPK ERK pathway.

phosphorylating the autophagy core protein *Beclin-1*, thereby dissociating its inhibitory complex with *Bcl-2*.[23] Additionally, tumor metabolic reprogramming research demonstrates that autophagy-mediated *glutaminolysis* suppresses oncogene *c-Myc* expression through *α-ketoglutarate*-dependent epigenetic modifications, forming a negative feedback loop to restrict *MAPK* pathway overactivation.[24]

In translational medicine, combination therapeutic strategies targeting the *MAPK/ERK* pathway have garnered significant attention. Preclinical experiments reveal that *MASM* synergistically enhances apoptotic effects when combined with autophagy inhibitors (eg, chloroquine), while its combination with conventional chemotherapeutic agents suppresses drug resistance by modulating cancer stem cell markers (eg, *Nanog, Oct-4*).[25] Furthermore, the development of nanodelivery systems (eg, pH-responsive liposomes) enables precise tumor targeting, improving *MASM* bioavailability

while reducing off-target toxicity.[26] These breakthroughs not only deepen the understanding of bidirectional regulatory mechanisms in the *MAPK/ERK* pathway but also provide new directions for developing precision therapies targeting autophagy-apoptosis synergy.

PI3K/AKT/mTOR Pathway: Overcoming Drug Resistance and Pro-Survival Inhibition

The phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (*PI3K/AKT/mTOR*) signaling pathway, a central hub regulating cell growth, metabolism, and survival, is not only a driver of tumorigenesis but also a key mechanism underlying chemotherapy resistance through its aberrant activation. Recent studies reveal that phosphorylation of *AKT* at *Ser473* drives downstream signaling networks via dual mechanisms (eg, *PDK1*-dependent activation and *mTORC2*-mediated feedback regulation). Matrine directly blocks *mTORC1* complex activity (composed of *mTOR* and *Raptor*) by specifically inhibiting this phosphorylation event, leading to dephosphorylation of downstream effectors *4E-BP1* and *S6K1*.(Figure 3) This suppresses ribosomal biogenesis and protein translation in *hepatocellular carcinoma (HCC)* cells, inducing *G1-phase* cell cycle arrest.[27] Notably, matrine's selective inhibition of *mTORC*1 activates the *AMPK-ULK1* axis, promoting autophagosome formation and enhancing autophagic flux. This process further compromises tumor cell metabolic adaptability by clearing misfolded proteins and damaged organelles.[28]

Exploration of combination therapies highlights the synergistic potential of targeting the *PI3K/AKT/mTOR* pathway. For instance, co-administration of matrine with the autophagy inducer rapamycin achieves dual *mTORC1* inhibition (directly targeted by rapamycin) and *AMPK* activation (mediated by matrine), significantly increasing tumor suppression rates to 75% in *HCC* models while reducing chemotherapy resistance-associated proteins (eg, *P-gp* and *BCL-2*).[29]

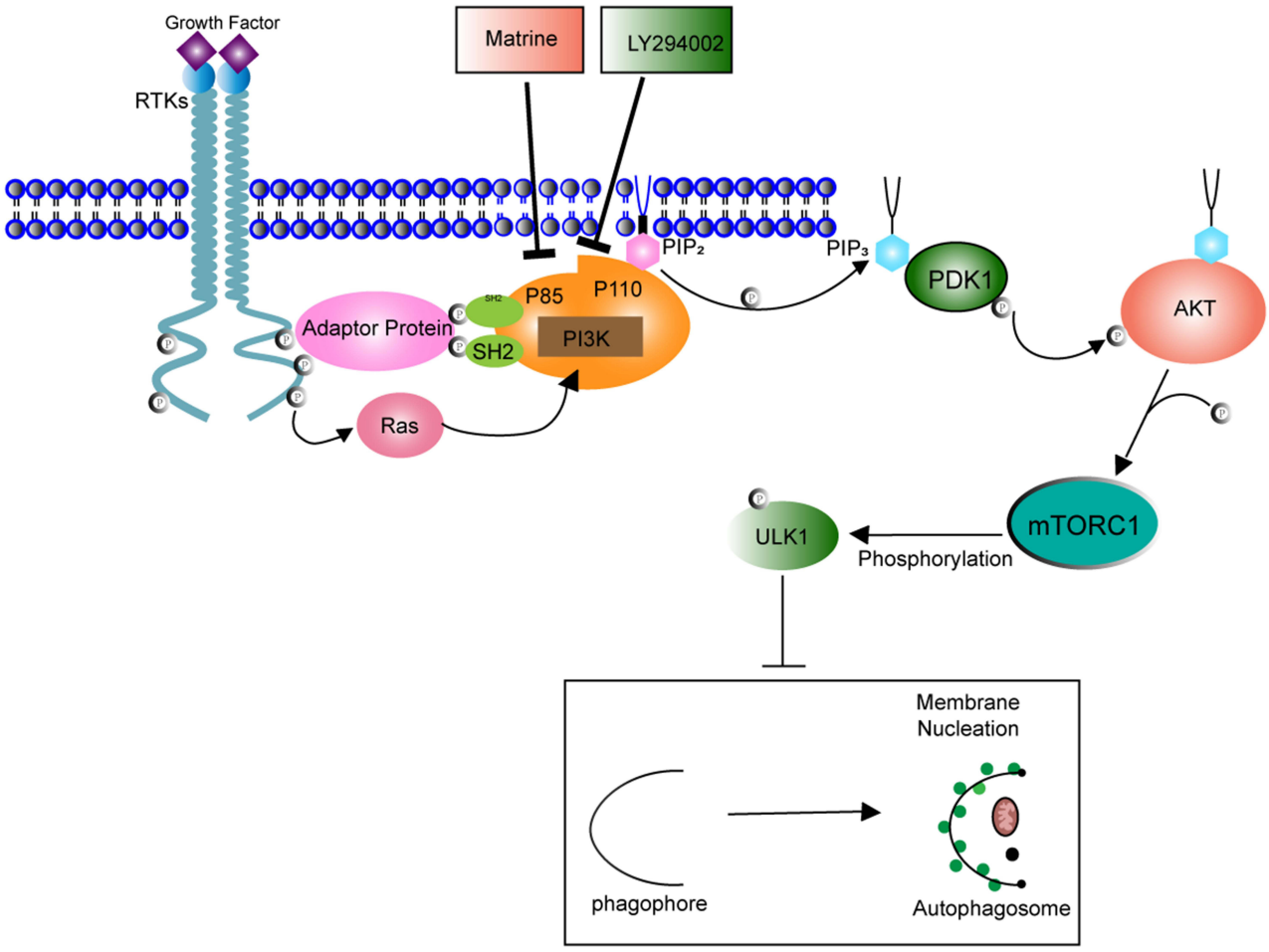

Figure 3 PI3K/AKT signaling pathway.

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Furthermore, emerging evidence indicates that PI3K/AKT/mTOR pathway inhibition reprograms tumor metabolic phenotypes: matrine reverses the *Warburg effect* by downregulating glycolytic enzymes *HK2* and *LDHA*, while suppressing *glutaminase (GLS1)* activity to block glutaminolysis. This results in decreased *α-ketoglutarate* levels, thereby inhibiting oncogene *c-Myc* transcription through epigenetic modifications (eg, *histone deacetylation)*.[30]

At the tumor microenvironment level, *PI3K/AKT/mTOR* pathway inhibition synergistically modulates immune responses. Matrine alleviates acidosis by reducing l*actate dehydrogenase A (LDHA*)-mediated lactate secretion, reversing the immunosuppressive function of M2-type *tumor-associated macrophages (TAMs)* and enhancing *CD8+ T* cell infiltration and activity.[31] This immunomodulatory role is particularly relevant in the context of immunologically "cold" tumors, such as ovarian cancer, where the complex *tumor immune microenvironment (TIME)* significantly contributes to the disappointing outcomes of immunotherapy. Advances in nanotechnology offer novel targeted delivery strategies. *pH*-responsive nanoparticles co-loaded with matrine and AKT-targeting *siRNA* enable selective drug release in *HCC* tissues while silencing AKT expression, significantly reducing extrahepatic toxicity and improving antitumor efficacy in vivo.[32] These breakthroughs not only elucidate the multidimensional roles of the *PI3K/AKT/mTOR* pathway in metabolic reprogramming and immune microenvironment regulation but also establish a theoretical foundation for developing precision therapies based on pathway crosstalk.[33] Future research should focus on exploring the interplay between this pathway, epigenetic modifications, and immune checkpoint inhibitors to overcome therapeutic challenges posed by tumor heterogeneity, particularly in cold tumors where reprogramming the TIME is crucial for enhancing treatment efficacy.

Pyroptosis Pathway: Enhancing Immunogenic Cell Death

Pyroptosis is an inflammatory programmed cell death mediated by the *Gasdermin (GSDM)* protein family, characterized by pore formation in the cell membrane via the N-terminal fragments of *Gasdermin* proteins. This process triggers cellular swelling, rupture, and the release of pro-inflammatory factors, thereby activating antitumor immune responses.[34] In the classical pathway, *pathogen-associated molecular patterns (PAMPs)* or *damage-associated molecular patterns (DAMPs)* activate inflammasomes (eg, *NLRP3*), recruiting *Caspase-1* to cleave *Gasdermin D (GSDMD)* and generate pore-forming N-terminal fragments, leading to IL-1β and IL-18 release.[35] The non-classical pathway involves intracellular *LPS* directly activating *Caspase-4/5/11* to cleave GSDMD and induce pyroptosis.[36] Additionally, in the exogenous apoptosis pathway, death receptors (eg, *TNF-α, FasL)* recruit Procaspase-8 through FADD, activating the Caspase-8/3 cascade to cleave *Gasdermin E (GSDME)* and form membrane pores.[37] Recent studies reveal that chemotherapeutic agents (eg, *5-FU, oxaliplatin*) induce pyroptosis via *Caspase-3/GSDME* axis activation, while radiotherapy enhances Gasdermin-mediated immunogenic death synergistically by triggering mitochondrial DNA leakage and activating the *cGAS-STING* pathway[38](Figure 4).

In *CRC* models, matrine combined with *5-FU* elevates pyroptosis rates through *Caspase-3/8*-dependent *GSDME* cleavage.[39] Pyroptotic cells release *IL-1β* and *HMGB1*, which activate *dendritic cell (DC) TLR4* signaling to promote tumor antigen cross-presentation and recruit *CD8+ T* cells and *NK* cells into the tumor microenvironment.[40] Concurrently, pyroptosis-induced *ATP* release binds to the *P2X7* receptor on macrophages, driving their polarization toward the pro-inflammatory *M1* phenotype and suppressing immunosuppressive regulatory *T cell (Treg)* function.[41] Notably, pyroptosis also activates the *cGAS-STING* pathway via *mitochondrial DNA (mtDNA)* release, inducing type I interferon secretion. This amplifies *DC* antigen presentation capacity, promotes *T cell* immune memory formation, and prolongs the duration of antitumor immune responses.[42]

Translational research on pyroptosis is now focusing on developing combination therapies. For instance, matrine enhances tumor cell sensitivity to *5-FU* by inhibiting *HDAC6* to upregulate *GSDME* expression, achieving remission in hepatocellular carcinoma models when combined with anti-PD-1 antibodies.[43] Moreover, nanodelivery systems can target tumor tissues to remodel the immune microenvironment synergistically with immune checkpoint inhibitors. Recent preclinical studies demonstrate that targeting key tumor metabolic enzymes (eg, *LDHA*) reduces lactate accumulation, reverses the immunosuppressive function of *M2* macrophages, and amplifies pyroptosis-mediated immune activation.[44] These advances not only highlight the central role of pyroptosis in cancer immunotherapy but also provide novel directions for developing precision therapies based on immunogenic cell death.

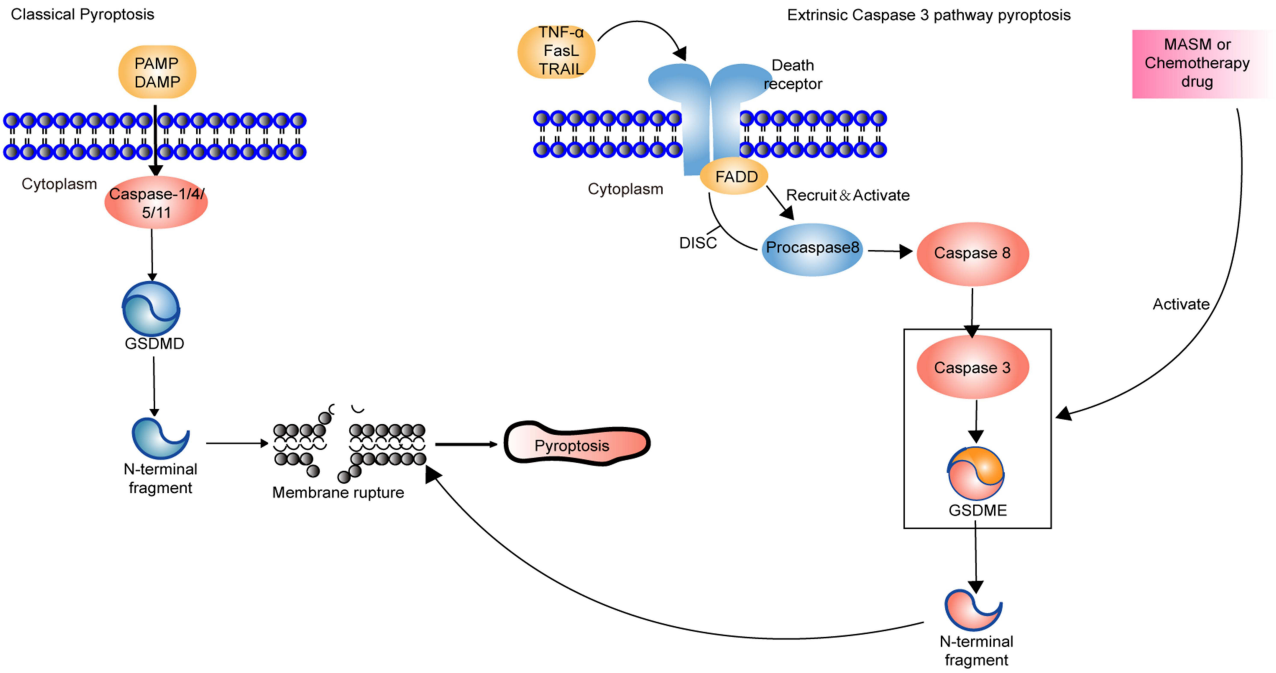

Figure 4 Classical Pyroptosis and Extrinsic Caspase 3 pathway Pyroptosis.

Cell Cycle Regulation: G2/M Phase Arrest

Dysregulation of the cell cycle constitutes a core feature of unlimited tumor proliferation. During the cell cycle, the *G2/M* phase represents the stage where cells prepare to enter mitosis, with its regulation being critical for cellular proliferation. Recent studies have revealed multiple mechanisms involved in *G2/M* phase regulation, including expression control of *Cyclin B1* and *CDK1*, activation of mitotic checkpoints, and the roles of cell cycle inhibitory factors.[45] As a natural plant-derived compound, matrine has demonstrated antitumor activity. In terms of cell cycle regulation, matrine induces *G2/M* phase arrest by downregulating *Cyclin B1* and *CDK1* expression, thereby inhibiting mitotic progression in hepatocellular carcinoma cells.[46] This discovery provides a novel therapeutic strategy for cancer treatment through targeted modulation of key cell cycle regulatory proteins to suppress tumor cell proliferation. In vitro experiments showed increased proportions of *G2/M* phase cells following 24-hour matrine treatment, indicating its effective interference with critical cell cycle checkpoints to block tumor cell proliferation.[47] Furthermore, studies have revealed matrine's capacity to activate apoptosis pathways, synergistically promoting tumor cell death.[48] In conclusion, cell cycle regulation targeting *G2/M* phase arrest represents a crucial therapeutic approach in oncology. Matrine, as a natural antitumor phytochemical, offers new strategic potential through its *Cyclin B1/CDK1*-mediated *G2/M* phase arrest mechanism. Future investigations should further explore matrine's clinical applications and molecular mechanisms in cancer therapeutics (Figure 5).

Advances in Preclinical Research and Translational Challenges

Recent preclinical studies on matrine and its derivatives in cancer therapy have revealed multidimensional mechanisms of action: The third-generation derivative *MT-26*, modified with sulfonic acid groups, enhances water solubility and achieves high tumor suppression rates in pancreatic cancer *PDX* models. Its core mechanism involves dual-target inhibition of *DNMT1/HDAC6*, inducing *RASSF1A* demethylation and activating the *NLRP3/caspase-1 pyroptosis* pathway.[49] In immunomodulation, Xiaozheng Yin combined with cisplatin reduces the *M2* macrophage ratio, a cell type recently shown to promote angiogenesis in tissue repair models via exosomal regulation of the *HIF1AN/HIF-1α/VEGFA* axis, drives a several-fold increase in *CD8+ T-cell* infiltration, and significantly prolongs disease-free survival in bladder cancer-bearing mice.[19] However, preclinical-to-clinical translation faces three major challenges (relevant to advancing toward human trials): Pharmacokinetically, first-pass effects (*CYP3A4* metabolic rate of 82%) and *P-gp-*

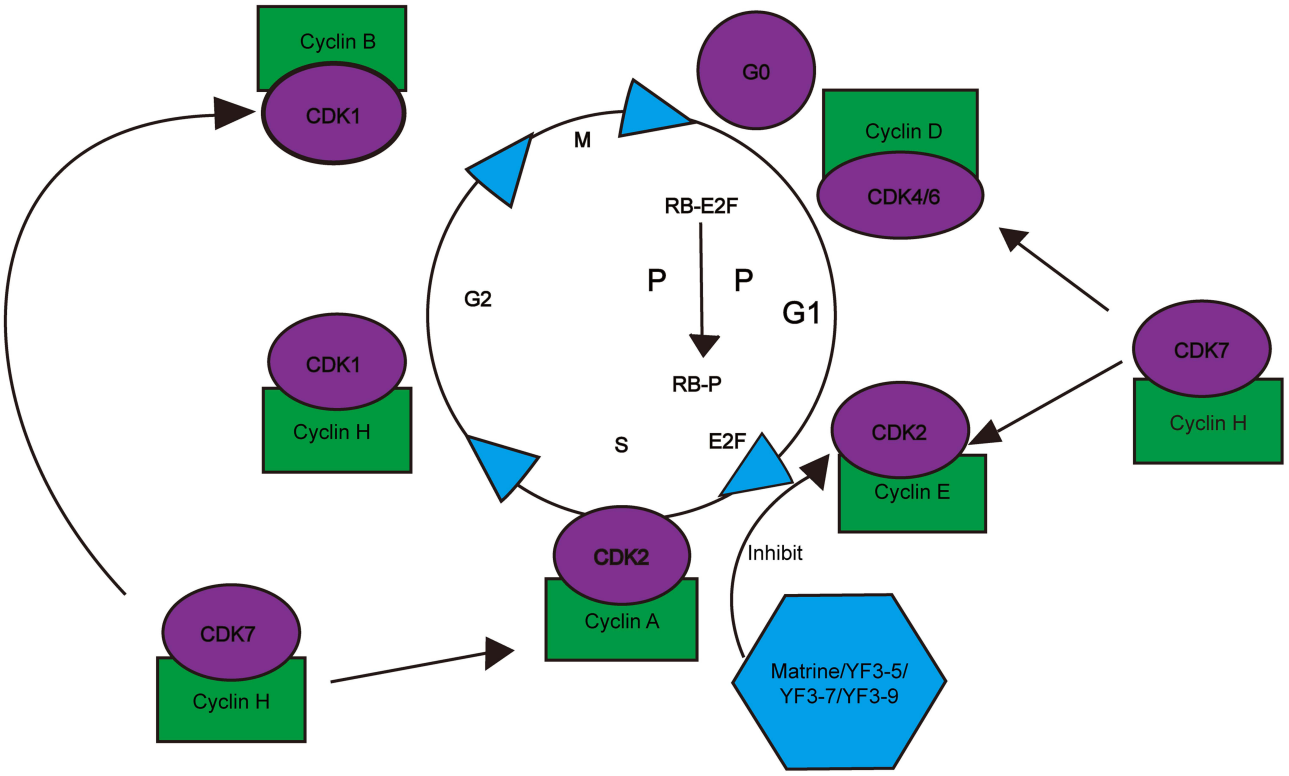

Figure 5 Schematic diagram of matrine action on the cell cycle.

mediated efflux result in extremely low oral bioavailability, while a volume of distribution (*Vd*) of 2.1 L/kg indicates risks of tissue accumulation.[50] Regarding off-target toxicity, high doses (>50 mg/kg) activate the *JNK/c-Jun* pathway, elevating hepatocyte *ALT/AST* levels by 2.3-fold, with single-cell sequencing revealing direct correlation with upregulated *Kupffer* cell *TLR4/MyD88* signaling.[51] For drug resistance, *SLC7A11*-mediated cystine uptake increases approximately twofold to counteract ferroptosis in *PDX* models—this mechanism may limit efficacy in human patients with high *SLC7A11* expression, highlighting the need for predictive biomarkers in future trials, while *CAF-secreted IL-6* elevates organoid *IC50* values by twofold.[52] Specifically, in *HepG2* human hepatocellular carcinoma cells treated with natural matrine (100 μM, 72 h), *SLC7A11* expression is upregulated by 2.3-fold, reducing lipid ROS accumulation by 40% and enabling ferroptosis evasion. In *PANC-1* pancreatic cancer cells, the third-generation derivative *MT-26* combined with erastin (a ferroptosis inducer) also faces resistance due to *SLC7A11* overexpression (1.8-fold vs parental cells), which abolishes the synergy between MT-26 and erastin. To address these bottlenecks, cutting-edge strategies demonstrate three breakthroughs: Smart delivery systems enhance targeted efficiency of anticancer nanodrugs via the EPR effect while maintaining intratumoral drug concentrations;[53] in precision combination therapy, co-administration with *GSK126* synergistically reduces *H3K27me3* modification, dramatically increasing apoptosis rates in ovarian cancer organoids; biomarker-driven research identifies *SLC39A7* deficiency-induced IC50 elevation and improved response rates in *RNF43*-mutated patients.[54] Notably, synthetic biology has significantly boosted matrine production yields while reducing costs.[55] Future advancements, leveraging *cryo-EM-resolved* Matrine-*CD36* complex structures,[56] will propel this field toward intelligent and precision-oriented therapeutic paradigms.

To date, no *phase I/II* clinical trials evaluating matrine or its derivatives (eg, *MT-26, YF-18*) in cancer patients have been registered or published. All current evidence for antitumor efficacy is derived from preclinical models (cell lines, *PDX* models, organoids), and "clinical translation challenges" discussed herein refer to barriers to advancing these preclinical findings into human trials (eg, low bioavailability, off-target toxicity).

Future Research Directions and Strategies

Multimodal Synergistic Therapy Enhancement System

In elucidating synergistic mechanisms, a three-dimensional deep learning framework can be constructed: The Transformer architecture integrates single-cell epigenomic profiles with drug molecular fingerprints,[57] identifying chromatin accessibility changes *post-EZH2* inhibition via contrastive learning. Cryo-electron tomography (*cryo-ET*) resolves dynamic conformations of *PD-1/Matrine* complexes, enabling spatial affinity prediction models.[58] The *Organoid Digital Twin (Organoid-DT)* system integrates light-sheet microscopy with machine learning algorithms[59] to quantify drug synergy indices. Recent studies confirm improved prediction accuracy in liver cancer organoids using the *DrugBAN* model based on heterogeneous graph neural networks.[60] This integrated computational-experimental approach represents a future strategy to move beyond empirical combination regimens toward rationally designed polytherapy. The justification lies in addressing tumor heterogeneity and adaptive resistance; for instance, single-cell multi-omics can reveal rare, resistant subpopulations that necessitate targeted co-therapy, while *Organoid-DT* systems allow for high-throughput testing of combination strategies across diverse genetic backgrounds. A key direction involves validating these predictions in immunocompetent organoid models that recapitulate tumor-immune crosstalk, ensuring translational relevance.

Intelligent Drug Delivery System Development

Novel carrier designs include: *DNA* origami nanorobots with *pH/ATP* dual-responsive modules;[61] magnetically controlled micro/nano-swimmers for blood-brain barrier penetration via ultrasound positioning and magnetic navigation;[62] quantum dot-encoded liposome libraries (*QDBODY* technology) for in vivo high-throughput screening, with real-time multi-formulation tracking through Raman spectroscopy.[63] Furthermore, natural polysaccharides with well-defined structures and intrinsic bioactivities, such as *BKP-1* from Bulbophyllum kwangtungense Schltr — which possesses a uniform molecular weight (1.92×10^6 Da) and a well-characterized skeletal structure of $\rightarrow$*4)-β-D-Xylp-(1*$\rightarrow^{4}$*-β-D-Xylp-(1]*$_4\rightarrow$*4)-α-D-GlcAp-(1*$\rightarrow^{4}$*-α-D-GlcAp-(1]*$_2\rightarrow$ — offer promising biopolymer foundations for constructing multifunctional delivery systems. The demonstrated anti-inflammatory activity of *BKP-1*, mediated via *NF-κB* pathway regulation, suggests its potential application in designing carrier systems that concurrently deliver drugs and modulate the tumor microenvironment to ameliorate inflammation-associated drug resistance.

The future strategy focuses on developing "theranostic" carriers that combine real-time biodistribution monitoring with targeted, condition-triggered drug release. This is justified by the need to overcome the physiological barriers (eg, elevated interstitial fluid pressure, dense stroma) that limit nanoparticle penetration into solid tumors. A promising direction involves engineering biomimetic nanoparticles coated with macrophage membranes to improve immune evasion and active targeting, thereby enhancing the therapeutic index of encapsulated matrine derivatives.

Precision Medicine-Driven Translational Research

Multi-omics integration requires breakthroughs: Spatial metabolomic mass spectrometry imaging (*Spatial-MSI*) deciphers spatial reprogramming of the glutamine-α-KG metabolic axis in tumor microenvironments under Matrine intervention.[64] Single-cell epi-drugomics *(scEpiDrug*) employs *CUT&Tag* technology to map chromatin response landscapes after *HDAC* inhibitor pretreatment.[65] Virtual response libraries for *patient-derived xenograft (PDX)* models leverage generative adversarial networks (*GANs*) to predict biomarker combinations.[66] The *DeepTCR* platform decodes relationships between *T-cell* receptor clonal evolution and drug responses.[67]

The overarching strategy here is to construct digital twins of patient tumors—computational models that simulate drug response based on individual multi-omics profiles. This is justified by the high failure rate of one-size-fits-all approaches in oncology. Future work must prioritize the development of explainable AI models that not only predict but also biologically interpret response signatures, facilitating the discovery of novel, mechanistically grounded biomarker combinations. Crucially, these models should be prospectively validated in basket trials that enroll patients based on molecular features rather than tumor histology.

Green Intelligent Manufacturing System Construction

Synthetic biology innovations encompass: Self-inducible expression systems using quorum sensing to regulate *CYP82* family modular assembly;[68] site-specific conjugation of non-natural amino acids to construct *Matrine-PROTAC* bifunctional molecules; blockchain-enabled continuous manufacturing platforms with real-time *critical quality attribute (CQA)* monitoring via spectroscopic PAT technology.[69] The *AI crystallization robot (CrystalGPT)* developed by *EPFL* enhances polymorph screening efficiency.[70] The strategic goal is to establish a sustainable, agile supply chain for matrine analogs, which is justified by the resource-intensive and ecologically taxing nature of traditional plant extraction. A key future direction involves engineering microbial consortia, where different modules of the complex biosynthetic pathway are distributed among specialized strains, thereby increasing overall yield and stability. Furthermore, the integration of *Life Cycle Assessment (LCA)* into the digital twin of the manufacturing process will be essential for quantitatively minimizing the environmental footprint from raw material to final product, aligning with green chemistry principles.

Smart Clinical Trial Paradigm Innovation

Implementation strategies include: *Metaverse patient recruitment systems (MetaTrial)* for rapid biomarker-positive cohort matching through digital phenotyping;[71] organ-on-chip/brain organoid platforms predicting neurotoxicity and off-target effects;[72] causal inference models (eg, *DoubleML*) for counterfactual efficacy estimation from real-world data, an *FDA*-approved method for supplementary clinical trial evidence.[73] Integrating quantum computing-assisted de novo drug design with 4D bioprinted tumor model validation, combined with transnational real-world databases from the *EU's* "Cancer Moonshot", may accelerate clinical translation of third-generation intelligent Matrine-based drugs and advance natural product *R&D*.[74] The core strategy is to create an adaptive, learning-based clinical trial ecosystem that continuously integrates preclinical and real-world evidence to optimize trial design and patient selection. This is justified by the prohibitive cost and time of conventional trials, especially for natural product derivatives which often face skepticism. A critical future direction is the wider adoption of platform trials and N-of-1 study designs, which can efficiently test multiple matrine-based candidates or combination regimens within a single, master protocol. Success hinges on establishing robust data standards and privacy-preserving federated learning frameworks across international regulatory agencies to enable the seamless use of real-world data as external control arms.

Conclusions

Matrine and its derivatives, as multi-target natural products, demonstrate synergistic antitumor effects by regulating core oncogenic pathways including *Wnt/β-catenin, MAPK/ERK*, and *PI3K/AKT/mTOR*, effectively suppressing tumor proliferation, inducing programmed cell death (apoptosis, autophagy, and pyroptosis), and remodeling the tumor microenvironment. Studies have revealed that matrine derivatives overcome chemoresistance through mechanisms such as dual inhibition of *DNMT1/HDAC6* and activation of the *NLRP3/caspase-1* pyroptosis pathway, showing remarkable efficacy in *PDX* models of pancreatic and liver cancers. However, preclinical-to-clinical translation faces critical challenges including pharmacokinetic limitations, off-target toxicity, and tumor heterogeneity-mediated drug resistance in preclinical models; importantly, no phase I/II clinical trials for these agents have been conducted to date. Future research should prioritize: developing intelligent delivery systems to enhance tumor targeting efficiency; integrating spatial metabolomics with single-cell epigenomic pharmacotyping to establish biomarker-guided precision therapeutics; optimizing biosynthesis pathways via synthetic biology and designing bifunctional molecules using *PROTAC* technology for enhanced efficacy; and implementing intelligent clinical trial paradigms based on organ-on-a-chip and digital twin technologies for patient-specific treatment optimization. Through interdisciplinary technological convergence and preclinical data optimization, matrine-based compounds have the potential to advance from preclinical research toward next-generation intelligent anticancer agents, pending successful resolution of current translational barriers.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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