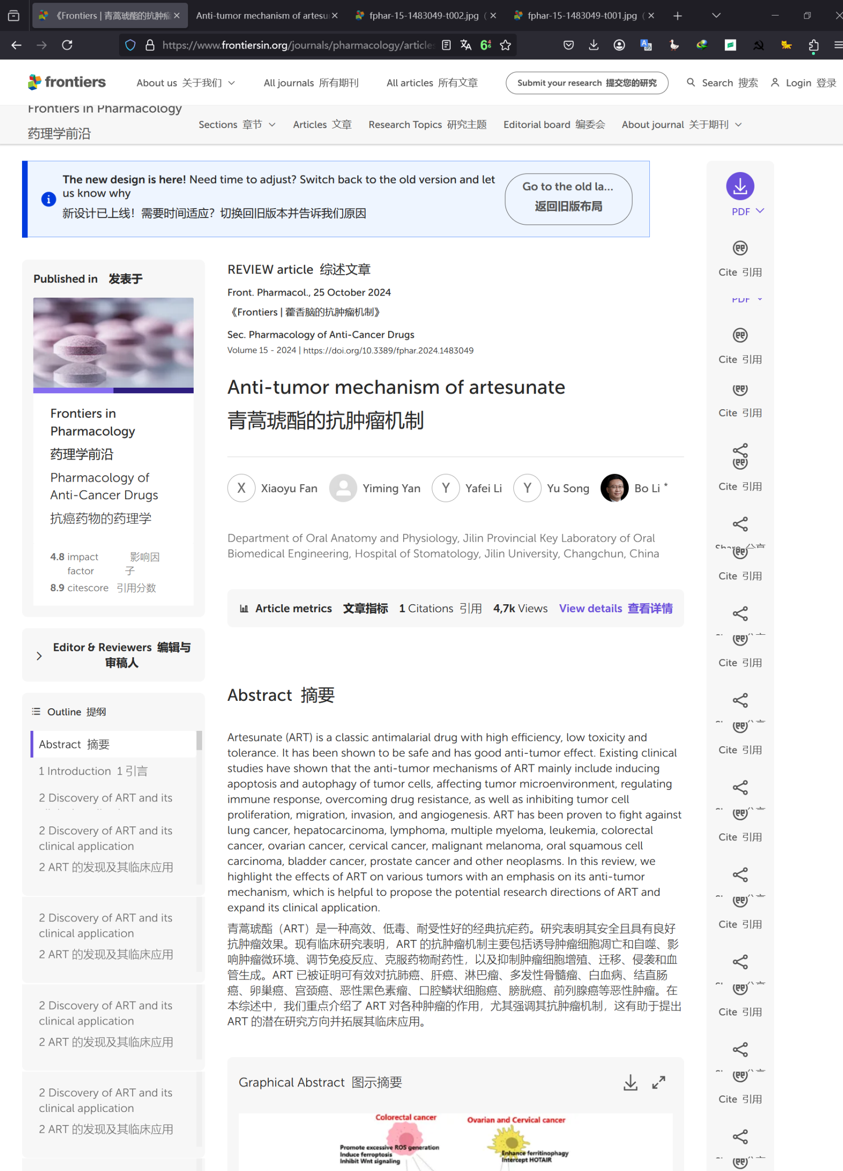
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REVIEW article 综述文章

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《Frontiers | 藿香脑的抗肿瘤机制》

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Anti-tumor mechanism of artesunate
青蒿琥酯的抗肿瘤机制

Xiaoyu Fan, Yiming Yan, Yafei Li, Yu Song, Bo Li *

Department of Oral Anatomy and Physiology, Jilin Provincial Key Laboratory of Oral Biomedical Engineering, Hospital of Stomatology, Jilin University, Changchun, China

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Abstract 摘要

Artesunate (ART) is a classic antimalarial drug with high efficiency, low toxicity and tolerance. It has been shown to be safe and has good anti-tumor effect. Existing clinical studies have shown that the anti-tumor mechanisms of ART mainly include inducing apoptosis and autophagy of tumor cells, affecting tumor microenvironment, regulating immune response, overcoming drug resistance, as well as inhibiting tumor cell proliferation, migration, invasion, and angiogenesis. ART has been proven to fight against lung cancer, hepatocarcinoma, lymphoma, multiple myeloma, leukemia, colorectal cancer, ovarian cancer, cervical cancer, malignant melanoma, oral squamous cell carcinoma, bladder cancer, prostate cancer and other neoplasms. In this review, we highlight the effects of ART on various tumors with an emphasis on its anti-tumor mechanism, which is helpful to propose the potential research directions of ART and expand its clinical application.

青蒿琥酯（ART）是一种高效、低毒、耐受性好的经典抗疟药。研究表明其安全且具有良好抗肿瘤效果。现有临床研究表明，ART 的抗肿瘤机制主要包括诱导肿瘤细胞凋亡和自噬、影响肿瘤微环境、调节免疫反应、克服药物耐药性，以及抑制肿瘤细胞增殖、迁移、侵袭和血管生成。ART 已被证明可有效对抗肺癌、肝癌、淋巴瘤、多发性骨髓瘤、白血病、结直肠癌、卵巢癌、宫颈癌、恶性黑色素瘤、口腔鳞状细胞癌、膀胱癌、前列腺癌等恶性肿瘤。在本综述中，我们重点介绍了 ART 对各种肿瘤的作用，尤其强调其抗肿瘤机制，这有助于提出 ART 的潜在研究方向并拓展其临床应用。

Graphical Abstract 图示摘要

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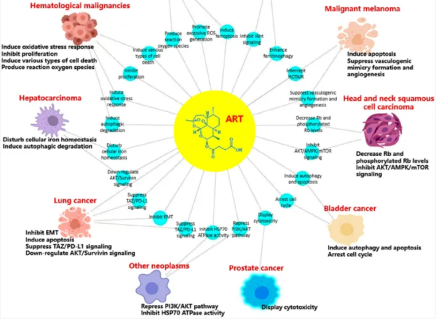
Hematological malignancies
Induce oxidative stress response
Inhibit proliferation
Induce various types of cell death
Produce reaction oxygen species
Malignant melanoma
Induce apoptosis
Suppress vasculogenic mimicry formation and angiogenesis
Hepatocarcinoma
Disturb cellular iron homeostasis
Induce autophagic degradation
Head and neck squamous cell carcinoma
Decrease Rb and phosphorylated Rb levels
Inhibit AKT/AMPK/mTOR signaling
ART
Produce reaction oxygen species
Promote excessive ROS generation
Induce ferroptosis
Inhibit Wnt signaling
Enhance ferritinophagy
Intercept HOTAIR
Induce various types of cell death
Inhibit proliferation
Induce oxidative stress response
Induce autophagic degradation
Disturb cellular iron homeostasis
Down-regulate AKT/Survivin signaling
Suppress TAZ/PD-L1 signaling
Suppress vasculogenic mimicry formation and angiogenesis
Decrease Rb and phosphorylated Rb levels
Inhibit AKT/AMPK/mTOR signaling
Induce autophagy and apoptosis
Arrest cell cycle
Display cytotoxicity
Inhibit EMT
Suppress TAZ/PD-L1 signaling
Inhibit HSP70 ATPase activity
Repress PI3K/AKT pathway
Lung cancer
Inhibit EMT
Induce apoptosis
Suppress TAZ/PD-L1 signaling
Down-regulate AKT/Survivin signaling
Bladder cancer
Induce autophagy and apoptosis
Arrest cell cycle
Other neoplasms
Repress PI3K/AKT pathway
Inhibit HSP70 ATPase activity
Prostate cancer
Display cytotoxicity

1 Introduction 1 引言

Chemoresistance is an important cause of tumor treatment failure and recurrence. Therefore, it is of great significance to find effective anti-tumor drugs that can overcome drug resistance. Artesunate (ART), an efficient and relatively safe water-soluble hemisuccinate derivative of dihydroartemisinin (DHA) (an antimalarial drug) (Qian Y. et al., 2021), is derived from artemisia annua. ART is inherently unstable in an aqueous solution, rapidly hydrolyzes after preparation and injection, and can be used for temporary intravenous administration (Gashe et al., 2022). At present, it has been found that two-carbon tied artemisinin-isatin complexes have anti-breast cancer potential and the artemisinin-isatin hybrid with ethylene binding system has anti-lung cancer activity (Wang et al., 2023a; Wang et al., 2023b). ART is inherently unstable in an aqueous solution, rapidly hydrolyzes after preparation and injection, and can be used for temporary intravenous administration. Recent studies have found that in addition to its specific anti-malaria effect, ART also has many other biological activities, such as anti-inflammatory (Ruwizhi et al., 2022), anti-tumor (Eitae and Park, 2020), anti-viral (Hu Y. J. et al., 2021) and hypoglycemic (Alagbonsi et al., 2021). Especially in the field of anti-tumor, several studies have reported the strong anticancer activity of ART in recent years (Ma et al., 2021; Guan et al., 2023; Zeng et al., 2023). The anti-tumor mechanism of ART is largely dependent on the release of DHA from ART as a prodrug. The latest research shows that DHA inhibits tumor progress via blocking ROR1-induced STAT3-activation (Li J.-Y et al., 2022; Li et al., 2024b), inhibits angiogenesis via regulating VEGF and MMP-2/-9 (Rao et al., 2024), remodels tumor micro-environment and improves cancer immunotherapy through inhibiting cyclin-dependent kinases (Zhou et al., 2024), restores the immunogenicity and enhances the anticancer immunosurveillance of cisplatin by activating the PERK/eIF$_2$α pathway (Li G et al., 2022). The other potential anti-tumor mechanisms of ART may be its own mechanism of action. ART inhibits the proliferation of Burkitt lymphoma cells by inhibiting AKT and ERK, so this compound is considered to have the potential to develop novel anti-tumor drugs (Yuan-Ce et al., 2023). Related studies have shown that ART acts on glioblastoma cells by inducing oxidative stress, DNA damage, apoptosis and necrosis (Strik et al., 2024). ART can also induce apoptosis of breast cancer cells, showing an anti-breast cancer effect (Wen et al., 2024). ART could combat choroidal melanoma by promoting apoptosis, inducing cell cycle arrest, and increasing intracellular ROS levels (Ma et al., 2024a). The review aims to exhibit the different mechanisms of ART against tumors, such as inhibiting proliferation and inducing apoptosis, and the latest research progress in different tumors elucidating the anti-tumor mechanism of ART, and lay a theoretical foundation for further development of ART therapy for cancer.

化疗耐药性是肿瘤治疗失败和复发的重要原因。因此，寻找能够克服耐药性的有效抗肿瘤药

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物具有重要意义。青蒿琥酯（ART）是双氢青蒿素（一种抗疟药）（Qian Y.等，2021）的一种高效且相对安全的水溶性半琥珀酸衍生物，来源于黄花蒿。ART 在水溶液中本身不稳定，制备和注射后迅速水解，可用于临时静脉注射（Gashe 等，2022）。目前，研究发现双碳连接的青蒿-异靛啉复合物具有抗乳腺癌的潜力，而具有乙烯结合系统的青蒿-异靛啉杂化物具有抗肺癌活性（Wang 等，2023a；Wang 等，2023b）。ART 在水溶液中本身不稳定，制备和注射后迅速水解，可用于临时静脉注射。 近期研究发现，除了其特定的抗疟效果外，青蒿素（ART）还具有多种其他生物活性，如抗炎（Ruwizhi 等，2022）、抗肿瘤（Eitae 和 Park，2020）、抗病毒（Hu Y. J.等，2021）和降血糖（Alagbonsi 等，2021）。特别是在抗肿瘤领域，近年来有多项研究报道了 ART 的强抗癌活性（Ma 等，2021；Guan 等，2023；Zeng 等，2023）。ART 的抗肿瘤机制很大程度上依赖于其作为前药的 DHA 释放。最新研究表明，DHA 通过阻断 ROR1 诱导的 STAT3 激活来抑制肿瘤进展（Li J.-Y 等，2022；Li 等，2024b），通过调节 VEGF 和 MMP-2/-9 来抑制血管生成（Rao 等，2024），通过抑制细胞周期依赖性激酶来重塑肿瘤微环境并改善癌症免疫治疗（Zhou 等，2024），通过激活 PERK/eIF$_2$α通路来恢复免疫原性并增强顺铂的抗癌免疫监视（Li G 等，2022）。ART 的其他潜在抗肿瘤机制可能与其自身的机制有关。 ART 通过抑制 AKT 和 ERK 来抑制伯基特淋巴瘤细胞的增殖，因此该化合物被认为具有开发新型抗肿瘤药物的潜力（Yuan-Ce 等，2023）。相关研究表明，ART 通过诱导氧化应激、DNA 损伤、凋亡和坏死作用于胶质母细胞瘤细胞（Strik 等，2024）。ART 也能诱导乳腺癌细胞凋亡，显示出抗乳腺癌作用（Wen 等，2024）。ART 可以通过促进凋亡、诱导细胞周期阻滞和增加细胞内 ROS 水平来对抗脉络膜黑色素瘤（Ma 等，2024a）。本综述旨在展示 ART 抗肿瘤的不同机制，如抑制增殖和诱导凋亡，以及阐明 ART 抗肿瘤机制的最新研究进展，为 ART 癌症治疗的进一步发展奠定理论基础。

2 Discovery of ART and its clinical application

2 ART 的发现及其临床应用

Artemisia annua is an anti-fever herbal medicine first described in traditional Chinese medicine 1,000 years ago. Artemisinin (ARS), the extract of Artemisia annua, and its derivatives (DHA, artemether, and ART) have been used for the treatment of malaria with substantial efficacy (**Zhang T. et al., 2020**). As a classic antimalarial drug, ART is widely used to treat malaria caused by the multidrug-resistant strains of *Plasmodium falciparum* (**Adebayo et al., 2020**) for its advantages of high potency, low toxicity (**Shi et al., 2022**), hydrophilic properties, better bioavailability than ARS (**Markowitsch et al., 2020**), and good tolerance without side effects (**Mancuso et al., 2021b**), which has broad development prospects. According to the results of relevant experiments, ART inhibits the growth and survival of many types of cancer including leukemia, melanoma cancer, bladder cancer, ovarian cancer, cervical cancer, breast cancer, colon cancer, head and neck tumors, hepatocellular carcinoma, prostate cancer, and multiple myeloma (**Hao et al., 2020**; **Ma and Fei, 2020**; **Wen et al., 2024**), etc. The role of ART against different cancers along with cell proliferation, apoptosis, western and IC50 can be observed from **Table 1**. For example, artesunate induces a decrease in Rb and phosphorylated Rb levels and thus promotes Head and neck squamous cell carcinoma (HNSCC) cell apoptosis (**Okamoto et al., 2023**). ART induces autophagy of tumor cells by activating AMPK-mTOR axis, which plays an anti-glioblastoma multiforme (GBM) role (**Ding et al., 2023**). Recent studies on the anti-tumor mechanism of ART have shown that ART produces ROS (**Zhao P. H. et al., 2020**) and causes apoptosis of cancer cells (**Yin et al., 2020**). Another study reveals that ART elevates the apoptotic rate and suppresses C918 cell (choroidal melanoma cells of the human eye) viability by regulating the MALAT1/YAP signaling pathway (**Jiu et al., 2021**). In addition, ART inhibits tumor invasion and metastasis by inhibiting angiogenesis and vasculogenic mimicry (VM) formation (**Geng et al., 2022**). ART has been shown to be safe (**Augustin et al., 2020**) and effective for clinical use, moreover, it has a wider range of potential clinical applications than originally hypothesized because of its greater biological activity (**Yang et al., 2021**).

青蒿是一种具有抗疟作用的草药，最早在 1000 年前被中医记载。青蒿素（ARS）是青蒿的提取物及其衍生物（DHA、蒿甲醚和 ART）被广泛用于治疗疟疾，并取得了显著疗效（Zhang T.等，2020）。作为经典的抗疟药物，ART 因其高效力、低毒性（Shi 等，2022）、亲水性、比 ARS 更好的生物利用度（Markowitsch 等，2020）以及良好的耐受性且无副作用（Mancuso 等，2021b）等特点，被广泛用于治疗由多药耐药性疟原虫引起的疟疾（Adebayo 等，2020），具有广阔的发展前景。根据相关实验结果，ART 能抑制多种类型癌症的生长和存活，包括白血病、黑色素瘤、膀胱癌、卵巢癌、宫颈癌、乳腺癌、结肠癌、头颈肿瘤、肝细胞癌、前列腺癌和多发性骨髓瘤（Hao 等，2020；Ma 和 Fei，2020；

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3 Antineoplastic mechanism of ART

3 Antineoplastic mechanism of ART
3 ART 的抗肿瘤机制

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3 ART 的抗肿瘤机制

3 Antineoplastic mechanism of ART
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Wen 等，2024）等。 ART 对不同癌症的作用、细胞增殖、凋亡、Western blot 和 IC50 值可以从表 1 中观察到。例如，青蒿素诱导 Rb 和磷酸化 Rb 水平的降低，从而促进头颈鳞状细胞癌（HNSCC）细胞凋亡（Okamoto 等，2023）。ART 通过激活 AMPK-mTOR 轴诱导肿瘤细胞自噬，发挥抗多形性胶质母细胞瘤（GBM）作用（Ding 等，2023）。近期关于 ART 抗肿瘤机制的研究表明，ART 产生 ROS（Zhao P. H.等，2020）并导致癌细胞凋亡（Yin 等，2020）。另一项研究表明，ART 通过调节 MALAT1/YAP 信号通路提高凋亡率，并抑制 C918 细胞（人眼脉络膜黑色素瘤细胞）的活力（Jiu 等，2021）。此外，ART 通过抑制血管生成和血管发生样形成（VM）来抑制肿瘤侵袭和转移（Geng 等，2022）。 ART 已被证明是安全的（Augustin 等人，2020 年）且对临床应用有效，此外，由于其更强的生物活性，它在临床应用上的潜在范围比最初假设的更广（Yang 等人，2021 年）。

TABLE 1 表 1

Neoplasms 肿瘤	Proliferation, invasion and metastasis 增殖、侵袭和转移	Apoptosis and autophagy 凋亡和自噬	Western blot	IC_{50} (μM)
Lung cancer 肺癌	Inhibit EMT, downregulate the transcription of MMP-2 and MMP-7 抑制上皮间质转化，下调 MMP-2 和 MMP-7 的转录	Regulate mitochondrial membrane potential 调节线粒体膜电位	Bcl-2 Bax	H1975:4.023 LLC:11.05 H468:16.11
Hepatocarcinoma 肝细胞癌	Alter the expression and	Target GBA, increase	Bcl-2 Bax	HepG2:38.38 MHCC-97H:1

The role of ART against different cancer along with other activities (cell proliferation/apoptosis/Western blot/IC50).

ART 对不同癌症的作用及其他活性（细胞增殖/凋亡/蛋白质印迹/IC50）。

3 Antineoplastic mechanism of ART

3 ART 的抗肿瘤机制

The main mechanism of ARS and its derivatives (ART, artemether, DHA) toward leukemia, multiple myeloma, and lymphoma cells comprises oxidative stress response, inhibition of proliferation, induction of various types of cell death as apoptosis, autophagy, ferroptosis, inhibition of angiogenesis, and signal transducers, such as NF-κB, MYC, amongst others (**Mancuso et al., 2021b**). Existing basic and clinical studies have shown that the pharmacological mechanism of ART therapy for cancer is embodied in the inhibition of tumor cell proliferation, migration and invasion (**Xu et al., 2022**), induction of tumor cell apoptosis and autophagy (**Zhao F. G. et al., 2020**), regulation of cell signal transduction (**Zeng et al., 2022**), inhibition of tumor angiogenesis (**Lu et al., 2022b**) and others (**Table 2**).

ARS 及其衍生物（ART、青蒿琥酯、DHA）对白血病、多发性骨髓瘤和淋巴瘤细胞的主要作用机制包括氧化应激反应、抑制增殖、诱导多种类型的细胞死亡（如细胞凋亡、自噬、铁死亡）、抑制血管生成以及信号转导（如 NF-κB、MYC 等）（Mancuso 等人，2021b）。现有的基础和临床研究表明，ART 癌症治疗的药理机制体现在抑制肿瘤细胞增殖、迁移和侵袭（Xu 等人，2022 年）、诱导肿瘤细胞凋亡和自噬（Zhao F. G.等人，2020 年）、调节细胞信号转导（Zeng 等人，2022 年）、抑制肿瘤血管生成（Lu 等人，2022b 年）等方面（表 2）。

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TABLE 2 表 2

Mechanism of action 作用机制	Signaling pathway 信号通路	References 参考文献
Inhibition of tumor cell proliferation, invasion and metastasis 抑制肿瘤细胞增殖、侵袭和转移	AMPK pathway, Akt/mTOR pathway, PI3K/AKT/FKHR pathway, MEK/ERK pathway, ERK/c-Myc pathway, STAT3 pathway, Wnt pathway AMPK 通路、Akt/mTOR 通路、PI3K/AKT/FKHR 通路、MEK/ERK 通路、ERK/c-Myc 通路、STAT3 通路、Wnt 通路	**Antoszczak et al. (2020), Chen et al. (2020), Wang et al. (2020a), Xiao et al. (2020), Yin et al. (2020), Berkoz et al. (2021), Hamoya et al. (2021), Li et al. (2021a), Hu et al. (2022), Huang et al. (2022a), Xu et al. (2022), Zhang et al. (2022e), Liu et al. (2023a)** Antoszczak 等(2020)、Chen 等(2020)、Wang 等(2020a)、Xiao 等(2020)、Yin 等(2020)、Berkoz 等(2021)、Hamoya 等(2021)、Li 等

Summary of antineoplastic mechanism and signaling pathway of artesunate.

青蒿琥酯的抗肿瘤机制和信号通路总结。

3.1 Inhibition of tumor cell proliferation, invasion and metastasis

3.1 抑制肿瘤细胞增殖、侵袭和转移

Studies have shown that ART can inhibit the proliferation of tumor cells by inhibiting or activating certain signal pathways (**Antoszczak et al., 2020**). ART causes mitochondrial dysfunction to further activate AMPK and suppress Akt/mTOR (**Xiao et al., 2020**). ART induces apoptosis in thyroid cancer cells and inhibits their proliferation and migration by inhibiting the PI3K/AKT/FKHR signal pathway (**Xu et al., 2022**). ART induces apoptosis of leukemia cells and inhibits the growth and stemness of transplanted tumors via the suppression of the MEK/ERK and PI3K/Akt pathways (**Chen et al., 2020**). ART evidently attenuates the migration, invasion and proliferation of cutaneous squamous cell carcinoma (CSCC) cells, which may be intensely related to PI3K/AKT pathway repression (**Huang X. Y. et al., 2022**). Another study proves that DHA and ART inhibit the growth of non-small cell lung cancer (NSCLC) via prohibiting cancer cell aerobic glycolysis through ERK/c-Myc pathway (**Zhang Y. X. et al., 2022**). ART can also inhibit cell proliferation, invasion and metastasis by affecting protein and enzyme expression. For instance, ART induces a significant downregulation of cyclin-dependent kinase-2 (CDK2), CDK4, cyclin D1, and cyclin E1 at various levels and then causes apoptosis, which impairs normal liver cell proliferation by inducing G0/G1 cell cycle arrest and apoptosis (**Yin et al., 2020**). ART combined with cisplatin (CIS) exerts anticancer effects on A549 cells by influencing the expression of Bcl-2, Box, p-P53, Caspase-3/7, Caspase-9, Cyclin Bl, P34, P21 (**Li W. et al., 2021**; **Liu W. et al., 2023**). The antimigration activity of ART is mediated by inhibition of BTBD7 mRNA expression while BTBD7 was found highly expressed in tumor tissues of NSCLC patients (**Wang J. S. et al., 2020**). ART may suppress the proliferation, migration and invasion of A549 and H1299 cells and induce their apoptosis by decreasing the expressions of human antigen R and matrix metalloproteinase-9 (MMP-9) proteins (**Hu et al., 2022**). The results obtained from another study demonstrate that the anticancer activity of ART occurs via STAT3 pathway and its target proteins (**Berkoz et al., 2021**). In addition, ART inhibits intestinal tumorigenesis by inhibiting Wnt signal pathway (**Hamoya et al., 2021**).

研究表明，青蒿琥酯（ART）可以通过抑制或激活某些信号通路来抑制肿瘤细胞的增殖（Antoszczak 等人，2020）。ART 导致线粒体功能障碍，进一步激活 AMPK 并抑制 Akt/mTOR（Xiao 等人，2020）。ART 通过抑制 PI3K/AKT/FKHR 信号通路诱导甲状腺癌细胞凋亡，并抑制其增殖和迁移（Xu 等人，2022）。ART 诱导白血病细胞凋亡，并通过抑制 MEK/ERK 和 PI3K/Akt 通路抑制移植肿瘤的生长和干性（Chen 等人，2020）。ART 明显减弱皮肤鳞状细胞癌（CSCC）细胞的迁移、侵袭和增殖，这可能与 PI3K/AKT 通路抑制密切相关

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（Huang X. Y.等人，2022）。另一项研究表明，DHA 和 ART 通过 ERK/c-Myc 通路禁止癌细胞有氧糖酵解来抑制非小细胞肺癌（NSCLC）的生长（Zhang Y. X.等人，2022）。ART 还可以通过影响蛋白质和酶的表达来抑制细胞增殖、侵袭和转移。 例如，青蒿琥酯（ART）在多个水平上显著下调细胞周期蛋白依赖性激酶-2（CDK2）、CDK4、细胞周期蛋白 D1 和细胞周期蛋白 E1 的表达，进而导致细胞凋亡，通过诱导 G0/G1 细胞周期阻滞和细胞凋亡来损害正常肝细胞增殖（Yin 等人，2020）。ART 与顺铂（CIS）联合通过影响 Bcl-2、Box、p-P53、Caspase-3/7、Caspase-9、细胞周期蛋白 Bl、P34、P21 的表达，对 A549 细胞产生抗癌作用（Li W.等人，2021；Liu W.等人，2023）。ART 的抑制迁移活性是通过抑制 BTBD7 mRNA 表达介导的，而 BTBD7 在非小细胞肺癌（NSCLC）患者的肿瘤组织中高度表达（Wang J. S.等人，2020）。ART 可能通过降低人抗原 R 和基质金属蛋白酶-9（MMP-9）蛋白的表达来抑制 A549 和 H1299 细胞的增殖、迁移和侵袭，并诱导其凋亡（Hu 等人，2022）。另一项研究获得的结果表明，ART 的抗癌活性是通过 STAT3 通路及其靶蛋白发生的（Berkoz 等人，2021）。此外，ART 通过抑制 Wnt 信号通路来抑制肠道肿瘤发生（Hamoya 等人，2021）。

3.2 Induction of tumor cell apoptosis and autophagy

3.2 诱导肿瘤细胞凋亡和自噬

ART evokes ferroptosis, an iron-dependent cell death caused by ROS formation (**Olivo et al., 2022**; **Huang et al., 2023**). Accordingly, ferroptotic effects have been demonstrated in ART-induced head and neck tumor cells, pancreatic cancer cells, liver cancer cells (**Markowitsch et al., 2020**), ovarian serous carcinoma cells (**Koike et al., 2022**) and glioblastoma cells (**Song et al., 2022**). ARS derivatives have been shown to have anti-NSCLC activity through induction of ROS-dependent apoptosis/ferroptosis (**Zhang Q. T. et al., 2021**). ART may induce apoptosis and cell cycle arrest to inhibit cell proliferation, and regulate autophagy and ferroptosis via impairing the STAT3 signaling pathway in diffuse large B cell lymphoma (DLBCL) cells (**Chen et al., 2021**). ART targets oral tongue squamous cell carcinoma via mitochondrial dysfunction-dependent oxidative damage (**Xiao et al., 2020**). ART treatment causes significant growth inhibition and apoptosis in A549 cells (**Zhang W. W. et al., 2022**) and induces apoptosis in breast cancer cells as a HSP70 ATPase activity inhibitor (**Pirali et al., 2020**). ART has an anti-esophageal cancer effect by inhibiting aerobic glycolysis (**Jin et al., 2022**). Furthermore, ART induces autophagy dependent apoptosis through upregulating ROS and activating AMPK-mTOR-ULK1 axis in human bladder cancer cells (**Zhou X. J. et al., 2020**). The researchers demonstrate that high GBA levels over activated autophagic flux, accelerates the rate at which cellular material may be degraded and recycled in balanced, healthy cells. This disturbance enables liver cancer to progress while ART can suppress GBA expression levels and restore normal autophagic flux, boosting the drug's anticancer activity (**Chen et al., 2022**).

ART 诱导铁死亡，这是一种由活性氧（ROS）形成引起的铁依赖性细胞死亡（Olivo 等人，2022 年；Huang 等人，2023 年）。因此，ART 诱导的头颈部肿瘤细胞、胰腺癌细胞、肝癌细胞（Markowitsch 等人，2020 年）、卵巢浆液性癌细胞（Koike 等人，2022 年）和胶质母细胞瘤细胞（Song 等人，2022 年）均表现出铁死亡效应。ARS 衍生物已被证明通过诱导 ROS 依赖性凋亡/铁死亡具有抗非小细胞肺癌（NSCLC）活性（Zhang Q.T.等人，2021 年）。ART 可能通过诱导凋亡和细胞周期阻滞来抑制细胞增殖，并通过损害弥漫性大 B 细胞淋巴瘤（DLBCL）细胞的 STAT3 信号通路来调节自噬和铁死亡（Chen 等人，2021 年）。ART 通过线粒体功能障碍依赖性氧化损伤靶向口腔鳞状细胞癌（Xiao 等人，2020 年）。ART 治疗对 A549 细胞（Zhang W.W.等人，2022 年）产生显著的生长抑制和凋亡，并作为 HSP70 ATP 酶活性抑制剂诱导乳腺癌细胞凋亡（Pirali 等人，2020 年）。ART 通过抑制有氧糖酵解具有抗食管癌作用（Jin 等人，2022 年）。 此外，ART 通过上调 ROS 并激活 AMPK-mTOR-ULK1 轴，在人类膀胱癌细胞中诱导自噬依赖性凋亡（Zhou X. J.等，2020）。研究人员表明，高 GBA 水平会过度激活自噬通量，加速平衡健康细胞中细胞物质的降解和回收速率。这种扰乱使肝癌得以进展，而 ART 可以抑制 GBA 表达水平并恢复正常的自噬通量，从而增强其抗癌活性（Chen 等，2022）。

3.3 Inhibition of tumor angiogenesis

3.3 抑制肿瘤血管生成

The mechanisms underlying tumor angiogenesis and VM formation involve hypoxia, EMT, and activation of tumor-associated fibroblasts and tumor-associated macrophages. Many molecules participate in one or more of these processes that regulate tumor angiogenesis, such as vascular endothelial growth factor (VEGF), MMPs, VE-cadherin, and non-coding RNAs (**Geng et al., 2022**) that emerged recently (**Figure 1**). Further, ART inhibits melanoma vasculogenic mimicry by inhibiting the HIF-1α/VEGF/PDGF pathway (**Ma et al., 2024b**). ART and other artemisinin derivatives have been identified as anti-

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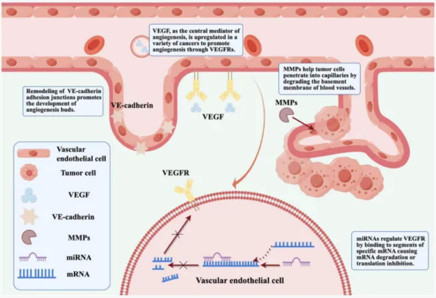
cancer agents due to their anti-proliferative, anti-angiogenic, and anti-inflammatory properties (**Zhong et al., 2021**). ART also inhibits STAT3 and Src activations and STAT3 related protein expressions. The upregulated expressions of STAT3 related protein by STAT3, play positive roles in melanoma metastasis through promoting cell invasion and angiogenesis (**Berkoz et al., 2021**). Currently, anti-angiogenesis targeting VEGFR-2 has been considered as an important strategy for cancer therapy (**Lu et al., 2022c**). ART inhibits choroidal melanoma cell growth through the STAT3/AKT signaling pathway (**Yao et al., 2024b**). Furthermore, the synergistic effect of ART and sorafenib (SOR) can inhibit non-Hodgkin lymphoma (NHL) cell viability and have anti-angiogenic activity. Further studies showed that gene inhibition of STAT3 could promote iron apoptosis and cell apoptosis induced by ART/SOR (**Chen Y. et al., 2023**).

肿瘤血管生成和血管生成样迁移形成的潜在机制涉及缺氧、上皮间质转化（EMT）以及肿瘤相关成纤维细胞和肿瘤相关巨噬细胞的激活。许多分子参与一个或多个这些调节肿瘤血管生成的过程，例如血管内皮生长因子（VEGF）、基质金属蛋白酶（MMPs）、VE-钙粘蛋白和最近出现的新型非编码 RNA（Geng 等人，2022 年）（图 1）。此外，青蒿素通过抑制 HIF-1α/VEGF/PDGF 通路抑制黑色素瘤血管生成样迁移（Ma 等人，2024b）。由于青蒿素及其它青蒿素衍生物具有抗增殖、抗血管生成和抗炎特性，已被鉴定为抗癌药物（Zhong 等人，2021）。青蒿素还抑制 STAT3 和 Src 的激活以及 STAT3 相关蛋白的表达。STAT3 上调的 STAT3 相关蛋白表达通过促进细胞侵袭和血管生成在黑色素瘤转移中发挥积极作用（Berkoz 等人，2021）。目前，靶向 VEGFR-2 的抗血管生成已被视为癌症治疗的重要策略（Lu 等人，2022c）。 ART 通过 STAT3/AKT 信号通路抑制脉络膜黑色素瘤细胞生长（Yao 等，2024b）。此外，ART 和索拉非尼（SOR）的协同作用可以抑制非霍奇金淋巴瘤（NHL）细胞的活力，并具有抗血管生成活性。进一步研究表明，STAT3 的基因抑制可以促进 ART/SOR 诱导的铁死亡和细胞凋亡（Chen Y.等，2023）。

FIGURE 1 图 1


VEGF, as the central mediator of angiogenesis, is upregulated in a variety of cancers to promote angiogenesis through VEGFRs.
MMPs help tumor cells penetrate into capillaries by degrading the basement membrane of blood vessels.
Remodeling of VE-cadherin adhesion junctions promotes the development of angiogenesis buds.
VE-cadherin
VEGF
MMPs
VEGFR
Vascular endothelial cell
Tumor cell
VEGF
VE-cadherin
MMPs
miRNA
mRNA
miRNAs regulate VEGFR by binding to segments of specific mRNA causing mRNA degradation or translation inhibition.
Vascular endothelial cell

VEGF, MMPs, VE-cadherin and non-coding RNA are involved in regulating the specific mechanisms of tumor angiogenesis (By Figdraw).

VEGF、MMPs、VE-cadherin 和非编码 RNA 参与调节肿瘤血管生成的特定机制（见图 draw）。

3.4 Affecting the tumor microenvironment

3.4 影响肿瘤微环境

The tumor microenvironment refers to the non-cancerous cells and the molecular components produced by the tumor. The interaction between tumor cells and tumor microenvironment plays an important role in tumor genesis, development, metastasis and response to therapy, which has attracted wide attention (**Xiao and Yu, 2021**). DHA (a metabolite produced in the liver from ART and artemether) regulates the crosstalk between autophagy and IFI16/caspase-1 inflammasome, which inhibits IL-1β production in tumor microenvironment (**Shi et al., 2020**). Furthermore, nanozyme-like single-atom catalyst combined with ART produces abundant cell cytotoxic radicals in tumor microenvironment (TME) for inhibiting tumor growth (**Lv et al., 2023**). Monocytes are components of the tumor microenvironment related to cancer progression and immune escape. ART induced changes in the monocyte phenotype are mediated by JAK2/STAT3 downregulation (**Mancuso et al., 2021c**).

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肿瘤微环境是指肿瘤产生的非癌细胞以及分子成分。肿瘤细胞与肿瘤微环境之间的相互作用在肿瘤发生、发展、转移以及对治疗的反应中起着重要作用，已引起广泛关注（Xiao 和 Yu，2021）。DHA（由 ART 和青蒿琥酯在肝脏中产生的代谢产物）调节自噬与 IFI16/caspase-1 炎症小体之间的相互作用，抑制肿瘤微环境中的 IL-1β产生（Shi 等人，2020）。此外，纳米酶样单原子催化剂与 ART 结合在肿瘤微环境（TME）中产生大量细胞毒性自由基，以抑制肿瘤生长（Lv 等人，2023）。单核细胞是肿瘤微环境中的组成部分，与癌症进展和免疫逃逸相关。ART 诱导的单核细胞表型变化由 JAK2/STAT3 下调介导（Mancuso 等人，2021c）。

3.5 Modulating immune response

3.5 调节免疫反应

ART has an immunomodulatory effect on various immune cells and cytokines of the immune system, also it shows different regulatory effects in different immune states (**Lin et al., 2022**). Flagella of tumor-targeting bacteria trigger local hemorrhage to reprogram tumor-associated macrophages for improved anti-tumor therapy (**Xu et al., 2023**). Other related studies report for the first time about the anti-complement bioactivities of ART and suggest a potential therapeutic benefit of ART in complement-related human diseases (**Song et al., 2021**). ART protects immunosuppression mice induced by glucocorticoids via enhancing pro-inflammatory cytokines release and bacterial clearance, and does indeed demonstrate to possess immunomodulatory effects (**Wang et al., 2021**). ART suppresses TAZ/PD-L1–induced T-cell growth inhibition *in vitro* and enhances anti-tumor immunity by recruiting infiltrating $CD8^+$ T-cells in syngeneic mouse models (**Cao et al., 2022**). NK cells can eliminate virus-infected cells and tumor cells nonspecifically (**Lin et al., 2022**) while ART is able to enhance the cytotoxicity of NK92 cells (**Zhang J. et al., 2021**; **Lin et al., 2022**).

ART 对免疫系统中的各种免疫细胞和细胞因子具有免疫调节作用，并且在不同的免疫状态下显示出不同的调节效果（Lin 等人，2022 年）。靶向肿瘤细菌的鞭毛触发局部出血，以重新编程肿瘤相关巨噬细胞，从而改善抗肿瘤治疗（Xu 等人，2023 年）。其他相关研究首次报道了 ART 的抗补体生物活性，并提出了 ART 在补体相关人类疾病中的潜在治疗益处（Song 等人，2021 年）。ART 通过增强促炎细胞因子的释放和细菌清除，保护由糖皮质激素诱导的免疫抑制小鼠，确实显示出具有免疫调节作用（Wang 等人，2021 年）。ART 在体外抑制 TAZ/PD-L1 诱导的 T 细胞生长抑制，并通过在同源小鼠模型中招募浸润的 $CD8^+$ T 细胞来增强抗肿瘤免疫（Cao 等人，2022 年）。NK 细胞可以非特异性地清除病毒感染细胞和肿瘤细胞（Lin 等人，2022 年），而 ART 能够增强 NK92 细胞的细胞毒性（Zhang J.等人，2021 年；Lin 等人，2022 年）。

3.6 Overcoming drug resistance in cancer cells

3.6 克服癌细胞耐药性

Overcoming drug resistance and seeking new therapeutic strategies are the main focus of tumor research. Natural products serve as effective substances against drug resistance because of their diverse chemical structures and pharmacological effects. Their main mechanisms for reversing resistance include regulating proteins involved in resistance, targeting non-apoptotic cell death, and inducing other types of non-apoptotic cell death. Signaling pathways associated with tumor resistance include epidermal growth factor receptor (EGFR), renin-angiotensin system (Ras), phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt), Wnt, Notch, transforming growth factor-β (TGF-β) and their specific natural product signaling pathway inhibitors. This has implications for how to prevent drug resistance to cancer treatment (**Yang et al., 2022**). Recent evidence shows that lysosomal function is associated with drug resistance of cancer cells. The results suggest that ART or other inhibitors of lysosomal function would be potential in the treatment of cancer cells with drug resistance caused by the enhanced lysosomal function (**Li Z. et al., 2021**). ART promotes anti-tumor immunity and overcomes EGFR-TKI resistance in non-small-cell lung cancer by enhancing oncogenic TAZ degradation (**Cao et al., 2022**). In addition, ART is effective against chemoresistant anaplastic thyroid carcinoma by targeting mitochondrial metabolism (**Ma and Fei, 2020**). Most patients with advanced HCC develop resistance to sorafenib early during treatment. While ART or ginsenoside Rg3 (a main bioactive triterpenoid saponin of red ginseng) in combination

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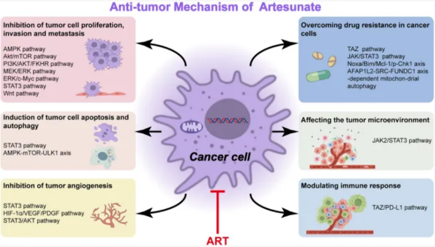
3 ART 的抗肿瘤机制
4 ART against different types of neoplasm
4 青蒿素对不同类型肿瘤的作用

with ART can be used to overcome resistance to Sorafenib in hepatocellular carcinoma cells (He et al., 2021; Yao et al., 2022). ART significantly inhibits proliferative and metabolic aspects of cisplatin-sensitive and cisplatin-resistant bladder cancer (BCa) cells, it may hold potential in treating advanced and therapy-resistant BCa (Zhao F. G. et al., 2020). ART reverses the resistance of AML cells to AraC by blocking the JAK/STAT3 signaling pathway, and the combination of ART and cytarabine significantly reduced the proliferation of AML cells and increased its apoptosis rate (Su et al., 2023). ART targeting Noxa/Bim/Mcl-1/p-Chk1 axis improves drug resistance of venetoclax combined with cytarabine in AML, providing a new triple therapy for AML treatment (Zhang J. et al., 2022). ART mitigates sorafenib resistance in hepatocellular carcinoma (HCC) patients by exacerbating AFAP1L2-SRC-FUNDC1 axis-dependent mitochondrial autophagy (Ma Z. et al., 2024) (Figure 2).

克服药物耐药性和寻求新的治疗策略是肿瘤研究的主要焦点。天然产物因其多样的化学结构和药理作用，成为对抗药物耐药性的有效物质。它们逆转耐药性的主要机制包括调节参与耐药性的蛋白质、靶向非凋亡性细胞死亡以及诱导其他类型的非凋亡性细胞死亡。与肿瘤耐药性相关的信号通路包括表皮生长因子受体（EGFR）、肾素-血管紧张素系统（Ras）、磷脂酰肌醇-3 激酶/蛋白激酶 B（PI3K/Akt）、Wnt、Notch、转化生长因子-β（TGF-β）及其特定的天然产物信号通路抑制剂。这涉及到如何预防癌症治疗中的药物耐药性（Yang 等人，2022）。近期证据表明，溶酶体功能与癌细胞耐药性相关。结果表明，ART 或其他溶酶体功能抑制剂在治疗因溶酶体功能增强引起的耐药性癌细胞方面具有潜力（Li Z.等人，2021）。ART 通过增强癌基因 TAZ 的降解促进抗肿瘤免疫并克服非小细胞肺癌中的 EGFR-TKI 耐药性（Cao 等人，2022）。此外，ART 通过靶向线粒体代谢对化疗耐药的未分化甲状腺癌有效（Ma 和 Fei，2020）。大多数晚期肝细胞癌患者在治疗早期就会对索拉非尼产生耐药性。ART 或人参皂苷 Rg3（红参的主要生物活性三萜皂苷）与 ART 联合使用可以克服肝细胞癌细胞对索拉非尼的耐药性（He 等人，2021；Yao 等人，2022）。ART 显著抑制了顺铂敏感性和顺铂耐药性膀胱癌（BCa）细胞的增殖和代谢方面，这可能使其在治疗晚期和难治性 BCa 方面具有潜力（Zhao F. G. 等人，2020）。ART 通过阻断 JAK/STAT3 信号通路逆转了 AML 细胞对 AraC 的耐药性，ART 和阿糖胞苷的联合使用显著降低了 AML 细胞的增殖并增加了其凋亡率（Su 等人，2023）。 ART 通过靶向 Noxa/Bim/Mcl-1/p-Chk1 轴，提高了维奈克拉联合阿糖胞苷治疗急性髓系白血病（AML）的耐药性，为 AML 治疗提供了一种新的三联疗法（Zhang J.等，2022）。ART 通过加剧 AFAP1L2-SRC-FUNDC1 轴依赖的线粒体自噬，减轻了肝细胞癌（HCC）患者的索拉非尼耐药性（Ma Z.等，2024）（图 2）。

FIGURE 2 图 2


Anti-tumor Mechanism of Artesunate
Inhibition of tumor cell proliferation, invasion and metastasis
AMPK pathway
Akt/mTOR pathway
PI3K/AKT/FKHR pathway
MEK/ERK pathway
ERK/c-Myc pathway
STAT3 pathway
Wnt pathway
Overcoming drug resistance in cancer cells
TAZ pathway
JAK/STAT3 pathway
Noxa/Bim/Mcl-1/p-Chk1 axis
AFAP1L2-SRC-FUNDC1 axis -dependent mitochon-drial autophagy
Induction of tumor cell apoptosis and autophagy
STAT3 pathway
AMPK-mTOR-ULK1 axis
Cancer cell
Affecting the tumor microenvironment
JAK2/STAT3 pathway
Inhibition of tumor angiogenesis
STAT3 pathway
HIF-1α/VEGF/PDGF pathway
STAT3/AKT pathway
ART
Modulating immune response
TAZ/PD-L1 pathway

Anti-tumor mechanism of artesunate. Some elements originate from Figdraw.

青蒿素的抗肿瘤机制。部分内容源自 Figdraw。

4 ART against different types of neoplasm

4 艾司 artesunate 对不同类型肿瘤的作用

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According to the latest estimates by the International Agency for Research on Cancer (IARC) through 2022, lung cancer was the most common cancer, followed by female breast, colorectal, prostate and stomach cancers. Lung cancer was also the leading cause of cancer death, followed by colorectal, liver, and female breast and stomach cancers. Broken down by sex, breast cancer and lung cancer were the most common cancers in women and men, respectively (**Bray et al., 2024**). Cancer is a major social, public health and economic problem of the 21st century. In the following, we focus on the role of artesunate in more than a dozen cancers, and present the latest trends and potential prospects for its prevention and control of tumors (**Table 3**; **Figures 3**, **4**).

根据国际癌症研究机构（IARC）截至 2022 年的最新估计，肺癌是最常见的癌症，其次是乳腺癌、结直肠癌、前列腺癌和胃癌。肺癌也是癌症死亡的首要原因，其次是结直肠癌、肝癌以及乳腺癌和胃癌。按性别划分，乳腺癌和肺癌分别是女性和男性的最常见癌症（Bray 等，2024）。癌症是 21 世纪重大的社会、公共卫生和经济问题。在下文中，我们重点关注青蒿素在十多种癌症中的作用，并展示其预防和控制肿瘤的最新趋势和潜在前景（表 3；图 3，图 4）。

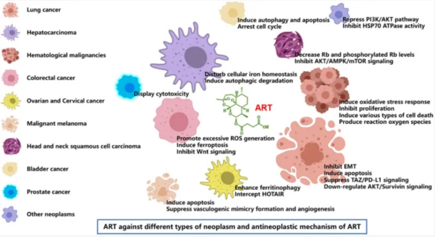
TABLE 3 表 3

Neoplasms 肿瘤	Mechanism of action 作用机制	References 参考文献
Lung cancer 肺癌	Inhibit EMT, regulate mitochondrial membrane potential, induce apoptosis, downregulate the AKT/ Survivin Signaling Pathway, suppress TAZ/PD-L1 signaling 抑制上皮间质转化，调节线粒体膜电位，诱导凋亡，下调 AKT/Survivin 信号通路，抑制 TAZ/PD-L1 信号	**Wang et al. (2020a), Zhao et al. (2020c), Cao et al. (2022) Zhang et al. (2022d), Somavarapu et al. (2023)** 王等 (2020a)，赵等 (2020c)，曹等 (2022) 张等 (2022d)，Somavarapu 等 (2023)
Hepatocarcinoma 肝癌	Disturb cellular iron homeostasis, target GBA and induce autophagic degradation	**Jiang et al. (2021), Chen et al. (2022)** 江等 (2021)，陈等 (2022)

Summary of the effects of artesunate on different neoplasms.

青蒿琥酯对不同肿瘤的作用总结。

FIGURE 3 图 3


Lung cancer
Hepatocarcinoma
Hematological malignancies
Colorectal cancer
Ovarian and Cervical cancer
Malignant melanoma
Head and neck squamous cell carcinoma
Bladder cancer
Prostate cancer
Other neoplasms
Induce autophagy and apoptosis
Arrest cell cycle
Repress PI3K/AKT pathway
Inhibit HSP70 ATPase activity
Decrease Rb and phosphorylated Rb levels
Inhibit AKT/AMPK/mTOR signaling
Disturb cellular iron homeostasis
Induce autophagic degradation
Display cytotoxicity
ART
Induce oxidative stress response
Inhibit proliferation
Induce various types of cell death
Produce reaction oxygen species
Promote excessive ROS generation
Induce ferroptosis
Inhibit Wnt signaling
Inhibit EMT
Induce apoptosis
Suppress TAZ/PD-L1 signaling
Down-regulate AKT/Survivin signaling
Enhance ferritinophagy
Intercept HOTAIR
Induce apoptosis
Suppress vasculogenic mimicry formation and angiogenesis
ART against different types of neoplasm and antineoplastic mechanism of ART

Artesunate inhibits growth and survival of many types of cancer including lung cancer, hepatocarcinoma, hematological malignancies, colorectal cancer, ovarian cancer, cervical cancer, malignant melanoma, head and neck tumor, bladder cancer, and prostate cancer. ART has the same or different mechanisms of action against different tumors, including the inhibition of tumor cell proliferation, migration and invasion [22], induction of tumor cell apoptosis and autophagy [23], regulation of cell signal transduction [24], inhibition of tumor angiogenesis [25] and many other

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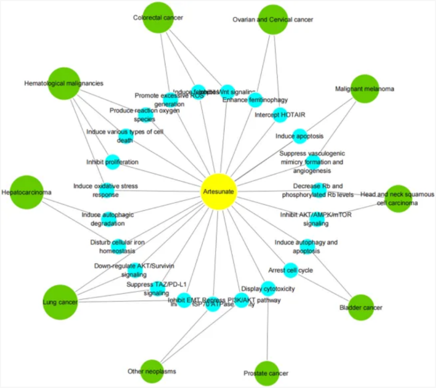
aspects.

青蒿琥酯抑制多种类型癌症的生长和存活，包括肺癌、肝细胞癌、血液系统恶性肿瘤、结直肠癌、卵巢癌、宫颈癌、恶性黑色素瘤、头颈肿瘤、膀胱癌和前列腺癌。ART 对不同肿瘤的作用机制相同或不同，包括抑制肿瘤细胞增殖、迁移和侵袭[22]，诱导肿瘤细胞凋亡和自噬[23]，调节细胞信号转导[24]，抑制肿瘤血管生成[25]以及其他方面。

FIGURE 4 图 4


Colorectal cancer
Ovarian and Cervical cancer
Hematological malignancies
Malignant melanoma
Promote excessive ROS generation
Induce ferroptosis
Inhibit Wnt signaling
Enhance ferritinophagy
Produce reaction oxygen species
Intercept HOTAIR
Induce various types of cell death
Induce apoptosis
Inhibit proliferation
Suppress vasculogenic mimicry formation and angiogenesis
Hepatocarcinoma
Induce oxidative stress response
Artesunate
Decrease Rb and phosphorylated Rb levels
Head and neck squamous cell carcinoma
Induce autophagic degradation
Inhibit AKT/AMPK/mTOR signaling
Disturb cellular iron homeostasis
Induce autophagy and apoptosis
Down-regulate AKT/Survivin signaling
Arrest cell cycle
Suppress TAZ/PD-L1 signaling
Display cytotoxicity
Lung cancer
Inhibit EMT
Repress PI3K/AKT pathway
HSP70 ATPase
Bladder cancer
Other neoplasms
Prostate cancer

Network of Artesunate's function in different types of neoplasm.

青蒿琥酯在不同类型肿瘤中的功能网络

4.1 Lung cancer 4.1 肺癌

Lung cancer is the main cause of cancer-related deaths around the world (**Sherry, 2022**). Recent studies have found that ART has significant therapeutic potential in multiple respiratory diseases (**Zhang et al., 2022b**). Lung cancer, the most common malignant tumor, is classified into NSCLC and small cell lung cancer (SCLC). ART was involved in inhibiting the epidermal interstitial transformation (EMT) of NSCLC cells by up-regulating the expression of epithelial marker E-cadherin and inhibiting the protein and mRNA levels of mesenchymal markers N-cadherin, vimentin and FN1 in A549 and H1975 cells (**Wang J. S. et al., 2020**). ART suppresses lung cancer cells growth by regulating mitochondrial membrane potential, inducing apoptosis (**Zhao et al., 2020c**) and down-regulating the AKT/Survivin Signaling Pathway (**Zhang W. W. et al., 2022**). In addition, ART enhances anti-tumor immunity and overcomes EGFR-TKI resistance in NSCLC at least in part by suppressing TAZ/PD-L1 signaling (**Cao et al., 2022**). Results have demonstrated that the ART-loaded PLGA porous microsphere could achieve excellent anti-cancer efficacy, providing a potential approach for NSCLC treatment via the pulmonary administration (**Xiong et al., 2021**). In addition, spray-dried micelles containing artesunate have the potential to be used as a dry powder formulation for inhalation in the treatment of lung cancer (**Somavarapu et al., 2023**).

肺癌是全球癌症相关死亡的主要原因（Sherry，2022）。近期研究表明，青蒿琥酯（ART）在多种呼吸系统疾病中具有显著的潜在治疗作用（Zhang 等人，2022b）。肺癌是最常见的恶性肿瘤，分为非小细胞肺癌（NSCLC）和小细胞肺癌（SCLC）。青蒿琥酯通过上调上皮标志物 E-钙粘蛋白的表达，并抑制 A549 和 H1975 细胞中基质标志物 N-钙粘蛋白、波形蛋白和 FN1 的蛋白和 mRNA 水平，参与了抑制 NSCLC 细胞的上皮间质转化（EMT）（Wang

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J.S.等人，2020）。青蒿琥酯通过调节线粒体膜电位、诱导细胞凋亡（Zhao 等人，2020c）和下调 AKT/Survivin 信号通路，抑制肺癌细胞生长（Zhang W.W.等人，2022）。此外，青蒿琥酯至少部分通过抑制 TAZ/PD-L1 信号通路，增强抗肿瘤免疫并克服 NSCLC 中的 EGFR-TKI 耐药性（Cao 等人，2022）。 结果表明，装载青蒿素的 PLGA 多孔微球能够实现优异的抗癌效果，为通过肺部给药治疗非小细胞肺癌提供了一种潜在方法（Xiong 等人，2021）。此外，含有青蒿素的喷雾干燥胶束有可能被用作治疗肺癌的吸入干粉制剂（Somavarapu 等人，2023）。

4.2 Hepatocarcinoma 4.2 肝癌

Hepatocellular carcinoma (HCC), one of the most common cancers, causes the fourth cancer-related deaths worldwide (**Wang M. Y. et al., 2020**). An effective strategy for HCC therapy is the perturbation of iron metabolism. ART regulates the unstable iron pool (LIP) and effectively induces ROS-dependent cell death in a variety of HCC cells, showing anticancer activity (**Jiang et al., 2021**). Glucosylceramidase (GBA) is required for autophagic degradation, and a preclinical study identified GBA as one of the direct targets of ART, which may have promising potential to inhibit lysosomal autophagy for HCC therapy (**Chen et al., 2022**). Another research shows that ART alone inhibits the proliferation of five HCC cell lines in a dose-dependent manner, and sorafenib combined with ART exert a synergistic anti-proliferation effect and induced synergistic apoptosis in HCC cell lines (**Yao et al., 2020**). The synergistic effects include ferroptosis induction (**Li Z. J. et al., 2021**), apoptosis induction, cell migration inhibition and anti-angiogenesis activity.

肝细胞癌（HCC）是最常见的癌症之一，全球每年有第四多的癌症相关死亡病例（Wang M. Y. 等人，2020）。HCC 治疗的有效策略是干扰铁代谢。青蒿琥酯（ART）调节不稳定的铁池（LIP），在各种 HCC 细胞中有效诱导 ROS 依赖性细胞死亡，显示出抗癌活性（Jiang 等人，2021）。葡萄糖脑苷脂酶（GBA）是自噬降解所必需的，一项临床前研究将 GBA 确定为 ART 的直接靶点之一，这可能具有抑制溶酶体自噬以治疗 HCC 的良好潜力（Chen 等人，2022）。另一项研究表明，ART 单独以剂量依赖性方式抑制五种 HCC 细胞系的增殖，而索拉非尼与 ART 联合发挥协同抗增殖作用，并在 HCC 细胞系中诱导协同凋亡（Yao 等人，2020）。协同作用包括铁死亡诱导（Li Z. J. 等人，2021）、凋亡诱导、细胞迁移抑制和抗血管生成活性。

4.3 Lymphoma, multiple myeloma and leukemia

4.3 淋巴瘤、多发性骨髓瘤和白血病

ARS and its derivatives (ART, DHA, artemether) act in a multi-specific manner against hematological malignancies, for example, lymphoma, multiple myeloma, and leukemia. The main mechanism of ARTs against different types of hematological malignancies comprises oxidative stress response, inhibition of proliferation, induction of various types of cell death (apoptosis, autophagy, ferroptosis, inhibition of angiogenesis), production of reaction oxygen species, induction of differentiation, and signal transducers, amongst others (**Li et al., 2020**; **Mancuso et al., 2021b**). ART is effective against adult T-cell leukemia/lymphoma by blocking G1 and/or G2/M phases, reducing the expression of cyclin-dependent kinases 1/2/4/6, cyclin B1/D2/E, and c-Myc, and increasing the expression of p21 (**Ishikawa et al., 2020**). ART exhibits cytotoxic effects in primary effusion lymphoma (**Ishikawa and Mori, 2021**) and induces apoptosis, autophagy and ferroptosis in diffuse large B cell lymphoma cells by impairing STAT3 signaling (**Chen et al., 2021**; **Chen et al., 2023a**). Beyond that, ART combined with arsenite inhibits the growth of multiple myeloma cells through the PI3K/AKT signaling pathway (**Hu G.-F. et al., 2021**). Leukemia is a hematological malignancy originated from the bone marrow (**Ng et al., 2021**). ART induces apoptosis and inhibits the proliferation, stemness, and tumorigenesis of leukemia (**Chen et al., 2020**). ART converts monocytes, a component of the tumor microenvironment associated with cancer progression and immune escape, into an inflammatory phenotype with the ability to kill leukemia cells (**Mancuso et al., 2021c**). Also, artesunate has significant anti-leukemia effects in mice by targeting ROS/Bim and TFRC/Fe^{2+} pathways (**Liu et al., 2023**). ART induces endoplasmic reticulum (ER) stress in leukemia cells eventually led to apoptosis (**Mancuso et al., 2021a**). Venetoclax plus cytarabine therapy is approved for elderly AML patients. Furthermore, ART induces synergistic apoptosis with venetoclax/cytarabine/

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daunorubicin accompanied (**Li J.-Y. et al., 2022**; **Zhang et al., 2022b**). Molecular docking findings reveal that artesunate is critically important in the therapy of AML due to its high affinity for the four primary disease targets, CASP3, EGFR, MAPK1, and STAT3 (**Tao et al., 2023**). Besides, ART induces cell death in pediatric AML cell lines through cytochrome c (**Hill et al., 2023**).

青蒿素及其衍生物（青蒿琥酯、二氢青蒿素、蒿甲醚）以多特异性方式作用于血液系统恶性肿瘤，例如淋巴瘤、多发性骨髓瘤和白血病。青蒿素类物质对不同类型血液系统恶性肿瘤的主要作用机制包括氧化应激反应、抑制增殖、诱导多种类型细胞死亡（凋亡、自噬、铁死亡、抑制血管生成）、产生反应性氧类、诱导分化以及信号转导等（Li 等，2020；Mancuso 等，2021b）。青蒿琥酯通过阻断 G1 和/或 G2/M 期、降低细胞周期蛋白依赖性激酶 1/2/4/6、细胞周期蛋白 B1/D2/E 和 c-Myc 的表达、增加 p21 的表达，对成人 T 细胞白血病/淋巴瘤有效（Ishikawa 等，2020）。青蒿琥酯在原发性渗出性淋巴瘤中表现出细胞毒性作用（Ishikawa 和 Mori，2021），并通过损害 STAT3 信号通路，在弥漫性大 B 细胞淋巴瘤细胞中诱导凋亡、自噬和铁死亡（Chen 等，2021；Chen 等，2023a）。此外，青蒿琥酯与砷结合可通过 PI3K/AKT 信号通路抑制多发性骨髓瘤细胞的生长（Hu G.-F.等，2021）。白血病是一种起源于骨髓的血源性恶性肿瘤（Ng 等，2021）。青蒿琥酯诱导白血病细胞凋亡，并抑制其增殖、干性和致瘤性（Chen 等，2020）。青蒿琥酯将单核细胞——这种与癌症进展和免疫逃逸相关的肿瘤微环境成分——转化为具有杀伤白血病细胞能力的炎性表型（Mancuso 等，2021c）。此外，青蒿琥酯通过靶向 ROS/Bim 和 TFRC/Fe $^{2+}$通路，在小鼠体内显示出显著的抗白血病作用（Liu 等，2023）。青蒿琥酯在白血病细胞中诱导内质网（ER）应激，最终导致细胞凋亡（Mancuso 等，2021a）。维奈克拉联合阿糖胞苷疗法已获批准用于老年急性髓系白血病（AML）患者。此外，青蒿琥酯与维奈克拉/阿糖胞苷/柔红霉素联合使用时可诱导协同凋亡（Li J.-Y.等，2022；Zhang 等，2022b）。分子对接研究结果表明，青蒿琥酯在急性髓系白血病（AML）治疗中至关重要，因为它对四种主要疾病靶点——CASP3、EGFR、MAPK1 和 STAT3——具有高度亲和力（Tao 等人，2023）。此外，ART 通过细胞色素 c 诱导儿童 AML 细胞系的细胞死亡（Hill 等人，2023）。

4.4 Colorectal cancer 4.4 结直肠癌

Colorectal cancer has the second highest incidence of malignant tumors and is the fourth leading cause of cancer deaths in China (**Cai et al., 2021**). The combination of Arte and 5-FU significantly reduced the viability of cancer cells *in vitro* and synergistically inhibited the growth of CRC xenografts *in vivo* (**Xia et al., 2023**). ART has been reported to be a promising candidate for CRC treatment, which induces senescence and autophagy to inhibit cell proliferation in colorectal cancer by promoting excessive ROS generation (**Huang Z. Y. et al., 2022**). The study proposes that ART induces cytotoxicity in HCT116 colon cancer cells by suppressing the expression of survivin and partially by ferroptosis (**Eitae and Park, 2020**). Abnormal Wnt signaling pathways are known to lead to unexpected β-catenin nuclear translocation and promote T-cell factor/lymphoid enhancer factor (TCF/LEF) transcriptional activity, resulting in CRC progression. ART inhibits intestinal tumorigenesis through inhibiting Wnt signaling (**Hamoya et al., 2021**).

结直肠癌是恶性肿瘤发病率第二高的癌症，也是中国癌症死亡的第四大原因（Cai 等人，2021）。Art 与 5-FU 的组合显著降低了体外癌细胞的活力，并协同抑制了体内结直肠癌异种移植物的生长（Xia 等人，2023）。ART 已被报道是治疗结直肠癌的潜在候选药物，它通过促进过度 ROS 生成来诱导衰老和自噬，从而抑制结直肠癌细胞的增殖（Huang Z. Y.等人，2022）。该研究提出，ART 通过抑制 survivin 的表达并部分通过铁死亡来诱导 HCT116 结肠癌细胞的细胞毒性（Eitae 和 Park，2020）。已知的异常 Wnt 信号通路会导致意外的β-catenin 核转位，并促进 T 细胞因子/淋巴样增强因子（TCF/LEF）转录活性，从而导致结直肠癌进展。ART 通过抑制 Wnt 信号通路来抑制肠道肿瘤发生（Hamoya 等人，2021）。

4.5 Ovarian cancer and cervical cancer

4.5 卵巢癌和宫颈癌

Ovarian cancer and cervical cancer are life-threatening diseases with a high mortality rate among women (**Caird et al., 2022**; **Yuan et al., 2022**). ART has preclinical activity in ovarian cancer that merits further investigation to treat ovarian cancer (**McDowell et al., 2021**). Enhancement of ferritinophagy is an important step involved in the mechanism of artesunate-induced ferroptosis, and ferritin heavy chain levels may contribute to the regulation of sensitivity in artesunate-induced ferroptosis in ovarian serous carcinoma cells (**Koike et al., 2022**). Synergetic delivery of ART and isosorbide 5-mononitrate with reduction-sensitive polymer nanoparticles for ovarian cancer chemotherapy (**Li et al., 2022b**). HOX transcript antisense RNA (HOTAIR), a trans-acting long non-coding RNA (lncRNA), plays an oncogenic role in cervical cancer by promoting cell proliferation, migration, invasion and autophagy, etc. Moreover, the blockade of HOTAIR by ART or propofol shows promise for further development of this lncRNA as a potential

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therapeutic target in cervical cancer (**Zhou et al., 2020a**). ART has a cytotoxic effect on squamous cells transformed by HPV. Self-administered vaginal ART inserts are safe and well-tolerated, which can be used at clinically effective doses to treat cervical intraepithelial neoplasia 2/3 (CIN2/3) (**Trimble et al., 2020**).

卵巢癌和宫颈癌是女性高致死率的生命威胁性疾病（Caird 等人，2022；Yuan 等人，2022）。青蒿琥酯在卵巢癌中具有临床前活性，值得进一步研究以治疗卵巢癌（McDowell 等人，2021）。增强铁蛋白自噬是青蒿琥酯诱导铁死亡机制中的重要步骤，铁蛋白重链水平可能有助于调节卵巢浆液性癌细胞中青蒿琥酯诱导的铁死亡敏感性（Koike 等人，2022）。将青蒿琥酯和异山梨酯单硝酸与减敏性聚合物纳米颗粒协同递送用于卵巢癌化疗（Li 等人，2022b）。HOX 转录反义 RNA（HOTAIR）是一种跨作用长非编码 RNA（lncRNA），通过促进细胞增殖、迁移、侵袭和自噬等作用在宫颈癌中发挥致癌作用。此外，青蒿琥酯或异丙酚阻断 HOTAIR 显示出作为宫颈癌潜在治疗靶点的进一步开发前景（Zhou 等人，2020a）。青蒿琥酯对由 HPV 转化而来的鳞状细胞具有细胞毒性。 自行使用的阴道 ART 置入剂安全且耐受性良好，可在临床有效剂量下用于治疗宫颈上皮内瘤变 2/3（CIN2/3）（Trimble 等，2020）。

4.6 Malignant melanoma 4.6 恶性黑色素瘤

Malignant melanoma is a malignant neoplasm of the skin and mucosal tissues (**Zahir et al., 2021**) characterized by a potential metastatic tumor of melanocytic origin. ART inhibits cellular proliferation of cancer cells by induction of apoptosis (**Wroblewska-Luczka et al., 2023**). The treatment shows decreased cellular migration, invasion, and colony formation in melanoma cells (**Berkoz et al., 2021**). ART suppresses choroidal melanoma (CM) vasculogenic mimicry formation and angiogenesis, while angiogenesis and VM are considered to be the main processes to ensure tumor blood supply during the proliferation and metastasis of CM (**Geng et al., 2022**). In uveal melanoma, ART elevates the apoptotic rate and suppresses C918 cell viability (**Jiu et al., 2021**). In addition, ART regulates the AKT/mTOR pathway by reducing the expression of Ang-1 in CM cells, thereby inhibiting the occurrence of CM tumors (**Yao et al., 2024a**). EphrinA3 (EFNA3) promotes CM cell growth and migration by activating the STAT3/AKT signaling pathway, while ART inhibits this process by down-regulating EFNA3 (**Yao et al., 2024a**). Meanwhile, ART has played a role in suppressing choroidal melanoma by regulating the HIF-1α/VEGF/PDGF pathway (**Ma et al., 2024b**).

恶性黑色素瘤是一种皮肤和黏膜组织的恶性肿瘤（Zahir 等人，2021 年），其特征是具有黑色素细胞来源的潜在转移性肿瘤。青蒿素通过诱导细胞凋亡抑制癌细胞增殖（Wroblewska-Luczka 等人，2023 年）。该治疗显示出黑色素瘤细胞中细胞迁移、侵袭和集落形成的减少（Berkoz 等人，2021 年）。青蒿素抑制脉络膜黑色素瘤（CM）血管生成拟态形成和血管生成，而血管生成和 VM 被认为是确保 CM 在增殖和转移过程中血液供应的主要过程（Geng 等人，2022 年）。在葡萄膜黑色素瘤中，青蒿素提高凋亡率并抑制 C918 细胞活力（Jiu 等人，2021 年）。此外，青蒿素通过降低 CM 细胞中 Ang-1 的表达来调节 AKT/mTOR 通路，从而抑制 CM 肿瘤的发生（Yao 等人，2024a）。EphrinA3（EFNA3）通过激活 STAT3/AKT 信号通路促进 CM 细胞生长和迁移，而青蒿素通过下调 EFNA3 抑制这一过程（Yao 等人，2024a）。 与此同时，青蒿琥酯通过调节 HIF-1α/VEGF/PDGF 通路在抑制脉络膜黑色素瘤方面发挥了作用（Ma 等人，2024b）。

4.7 Head and neck squamous cell carcinoma

4.7 头颈部鳞状细胞癌

Artesunate and cisplatin synergistically inhibit HNSCC cell growth and promote apoptosis with artesunate-induced decreases in Rb and phosphorylated Rb levels (**Okamoto et al., 2023**). Oral squamous cell carcinoma, the most common type of oral cancer, affects more than 275,000 people per year worldwide (**Pena-Oyarzun et al., 2020**). ARS suppresses tumor growth and induces vascular normalization in oral squamous cell carcinoma via inhibition of macrophage migration inhibitory factor (**Ding et al., 2019**; **Yu et al., 2024**). Mitochondrial metabolism has recently gained attention as a promising therapeutic strategy in cancer. ART targets oral tongue squamous cell carcinoma via mitochondrial dysfunction-dependent oxidative damage and Akt/AMPK/mTOR inhibition (**Xiao et al., 2020**).

青蒿琥酯和顺铂协同抑制头颈部鳞状细胞癌（HNSCC）细胞生长并促进凋亡，这与青蒿琥酯引起的 Rb 和磷酸化 Rb 水平降低有关（Okamoto 等人，2023）。口腔鳞状细胞癌是口腔癌中最常见的类型，每年影响全球超过 275,000 人（Pena-Oyarzun 等人，2020）。青蒿琥酯通过抑制巨噬细胞迁移抑制因子（MIF）来抑制口腔鳞状细胞癌的生长并诱导血管正常化（Ding 等人，2019；Yu 等人，2024）。线粒体代谢最近作为癌症治疗的一种有前景的策略而受到关注。青蒿琥酯通过线粒体功能障碍依赖的氧化损伤和 Akt/AMPK/mTOR 抑制靶向口腔舌鳞状细胞癌（Xiao 等人，2020）。

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4.8 Bladder cancer 4.8 膀胱癌

Urinary bladder cancer is a common urological cancer (Tse et al., 2021) and is the 10th most common cancer type in the world (Bilim et al., 2022). ART can inhibit the viability, proliferation and migration of bladder cancer cells, as well as induce autophagy in a time and dose dependent manner. In addition, ART induced apoptosis of bladder cancer cells by up-regulating ROS and activating AMPK-mTOR-ULK1 pathway (Zhou X. J. et al., 2020). ART impairs growth in cisplatin-resistant bladder cancer cells by cell cycle arrest, apoptosis and autophagy induction, which may hold potential in treating advanced and therapy-resistant bladder cancer (Zhao F. G. et al., 2020). ART induces G2/M cell cycle arrest in HT 1376 and BFTC 909 cell lines, thereby inducing apoptosis and REDOX imbalance, and may be a candidate drug for the treatment of bladder cancer in concert with cisplatin (Chen S. Y. et al., 2023). A new artesunate-metformin dimer triazine derivative AM2 is designed and synthesized by coupling artesunate with metformin. AM2 inhibits the growth of bladder cancer cells T24 by inhibiting cellular adipogenesis associated with the Clusterin/SREBP1/FASN signaling pathway (Lin et al., 2024).

尿路上皮癌是一种常见的泌尿系统癌症（Tse 等人，2021 年），全球第 10 大常见癌症类型（Bilim 等人，2022 年）。青蒿琥酯可以抑制膀胱癌细胞的活力、增殖和迁移，并以时间和剂量依赖的方式诱导自噬。此外，青蒿琥酯通过上调 ROS 和激活 AMPK-mTOR-ULK1 通路诱导膀胱癌细胞凋亡（Zhou X. J.等人，2020 年）。青蒿琥酯通过细胞周期阻滞、凋亡和自噬诱导损害顺铂耐药膀胱癌细胞的生长，这可能为治疗晚期和难治性膀胱癌提供潜在价值（Zhao F. G.等人，2020 年）。青蒿琥酯在 HT 1376 和 BFTC 909 细胞系中诱导 G2/M 细胞周期阻滞，从而诱导凋亡和氧化还原失衡，可能成为与顺铂联合治疗膀胱癌的候选药物（Chen S. Y.等人，2023 年）。通过将青蒿琥酯与二甲双胍偶联，设计并合成了新型青蒿琥酯-二甲双胍二聚体三嗪衍生物 AM2。 AM2 通过抑制与 Clusterin/SREBP1/FASN 信号通路相关的细胞脂肪生成来抑制膀胱癌细胞 T24 的生长（Lin 等人，2024）。

4.9 Prostate cancer 4.9 前列腺癌

Prostate cancer (PC), a malignant tumor occurring in the male prostate, is the second leading cause of cancer-related deaths in men. The lesions have the characteristics of small size and blurry outline (Qian Y. J. et al., 2021). Combining ART with PTX displays cytotoxicity regardless of the type of prostate cancer cell line. This may offer a promising new therapeutic option for the treatment of metastatic hormone-refractory PC (Adedeji et al., 2020; Fabian et al., 2022). ART induced apoptosis of parent and DX-resistant DU145 cells by increasing ROS, indicating that ART inhibited the growth of docetaxel-resistant PC cells (Vakhrusheva et al., 2022).

前列腺癌（PC）是男性前列腺发生的恶性肿瘤，是男性癌症相关死亡的第二主要原因。病变具有体积小、轮廓模糊的特点（Qian Y. J.等人，2021）。ART 与 PTX 结合显示出细胞毒性，无论前列腺癌细胞系的类型如何。这可能为转移性激素难治性前列腺癌的治疗提供一种有前景的新治疗选择（Adedeji 等人，2020；Fabian 等人，2022）。ART 通过增加 ROS 诱导亲本和 DX 耐药的 DU145 细胞凋亡，表明 ART 抑制了多西他赛耐药前列腺癌细胞生长（Vakhrusheva 等人，2022）。

4.10 Other neoplasms 4.10 其他肿瘤

ART evidently attenuates the migration, invasion and proliferation, lessened cell numbers at G2/M phase and triggers apoptosis of CSCC cells, which may be intensely related to the PI3K/AKT pathway repression (Huang X. Y. et al., 2022). ART induces the death of breast cancer cell lines 4T1 and MCF-7 by inhibiting the expression of HSP70 and Bcl-2 (Pirali et al., 2020; Svolacchia et al., 2023). ART targets HK1, promotes the degradation of HK1, reduces the expression of HIF-1α and PKM2, which are key glycolytic enzymes, and plays an anti-EC role (Jin et al., 2022). Furthermore, ART can reverse gemcitabine (dFdC) resistance in combination with dFdC in dFdC-resistant Panc-1 cells *in vitro* (Yao et al., 2022b). ART therapy significantly increases the cytotoxicity of Sunitinib-resistant RCC cells and inhibited proliferation and clonal growth. ART inhibits the growth of KAKI-1, 786-O, and A-498 cell lines through G0/G1 phase arrest and significant regulation of cell cycle regulators, and inhibits the growth of KTCTL-26 through ROS production, ferroptosis, and metabolism (Markowitsch et al., 2020). The inhibition of ART on chemotherapy-sensitive (8505C and KAT-4) and drug-resistant (8505C-R and KAT-4-R) ATC cells is effective against chemotherapy-resistant anaplastic thyroid cancer by inhibiting mitochondrial function, leading to oxidative stress and damage (Ma and Fei, 2020). ART inhibits apoptosis, proliferation and migration of thyroid cancer cells by inhibiting the PI3K/AKT/FKHR signaling pathway (Xu et al., 2022). ART exerts anti-prolactinoma activity by inducing G0/G1 phase arrest and cell apoptosis, thereby

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inhibiting mitochondrial metabolism and inducing cell apoptosis (**Zhang W. Y. et al., 2020**). ART influences iron apoptosis by regulating iron homeostasis and p38 and ERK signaling pathways. These findings support the role of ART in inducing ferroptosis through this pathway in glioblastoma (**Song et al., 2022**). In breast cancer, artesunate also induces apoptosis in cancer cells (**Wen et al., 2024**).

ART 明显减弱了迁移、侵袭和增殖，降低了 G2/M 期细胞数量，并触发了 CSCC 细胞的凋亡，这可能与 PI3K/AKT 通路抑制密切相关（Huang X. Y.等，2022）。ART 通过抑制 HSP70 和 Bcl-2 的表达，诱导了乳腺癌细胞系 4T1 和 MCF-7 的死亡（Pirali 等，2020；Svolacchia 等，2023）。ART 靶向 HK1，促进 HK1 的降解，降低关键糖酵解酶 HIF-1α和 PKM2 的表达，发挥抗 EC 作用（Jin 等，2022）。此外，ART 可以逆转 dFdC 耐药性，与 dFdC 联合使用时，在耐药的 Panc-1 细胞中显示出体外逆转效果（Yao 等，2022b）。ART 治疗显著增加了 Sunitinib 耐药性 RCC 细胞的细胞毒性，并抑制了增殖和克隆生长。ART 通过 G0/G1 期阻滞和显著调节细胞周期调节因子，抑制了 KAKI-1、786-O 和 A-498 细胞系的生长，并通过 ROS 产生、铁死亡和代谢抑制了 KTCTL-26 的生长（Markowitsch 等，2020）。 ART 对化疗敏感（8505C 和 KAT-4）和耐药（8505C-R 和 KAT-4-R）的 ATC 细胞具有抑制作用，通过抑制线粒体功能，导致氧化应激和损伤，从而有效对抗化疗耐药的未分化甲状腺癌（Ma 和 Fei，2020）。ART 通过抑制 PI3K/AKT/FKHR 信号通路，抑制甲状腺癌细胞的凋亡、增殖和迁移（Xu 等，2022）。ART 通过诱导 G0/G1 期阻滞和细胞凋亡，发挥抗催乳素瘤活性，从而抑制线粒体代谢并诱导细胞凋亡（Zhang W. Y.等，2020）。ART 通过调节铁稳态和 p38 及 ERK 信号通路，影响铁凋亡。这些发现支持 ART 通过该通路在胶质母细胞瘤中诱导铁死亡的作用（Song 等，2022）。在乳腺癌中，青蒿琥酯也诱导癌细胞凋亡（Wen 等，2024）。

5 Clinical evidence of ART as an anti-cancer therapy

5 ART 作为抗癌治疗的临床证据

At present, artesunate has been gradually used in clinical studies to treat tumors, and has become a promising strategy for the treatment of cancer. In glioblastoma cells, artesunate acts as a supplement for cancer treatment. Clinical trials have shown that artesunate itself is cytotoxic and enhances the cytotoxicity of temozolomide, and therefore has the potential to enhance the therapeutic efficacy of glioblastoma (**Strik et al., 2024**). Artesunate is effective, safe and well tolerated for the treatment of cervical intraepithelial neoplasia 2/3 (CIN2/3) (**Trimble et al., 2020**). Phase I clinical trials evaluated artesunate suppositories as effective in treating HPV-infected cells with cytotoxic effects while having minimal effects on healthy cells (**Fang et al., 2023**). Artesunate has shown anticancer activity both *in vitro* and *in vivo* against hematological malignancies in a multispecific manner. The main mechanisms of its action on leukemia, multiple myeloma and lymphoma cells include oxidative stress response, inhibition of proliferation and induction of various types of cell death (**Li et al., 2020**; **Mancuso et al., 2021b**). Because artesunate drugs are highly effective and well tolerated without side effects, they could be applied in the future as anti-tumor therapy alone or in combination with standard chemotherapy after further clinical trials in various tumors are completed.

目前，青蒿琥酯已逐渐用于临床研究治疗肿瘤，并成为癌症治疗的一种有前景的策略。在胶质母细胞瘤细胞中，青蒿琥酯作为癌症治疗的补充剂。临床试验表明，青蒿琥酯本身具有细胞毒性，并能增强替莫唑胺的细胞毒性，因此有可能提高胶质母细胞瘤的治疗效果（Strik 等人，2024）。青蒿琥酯在治疗宫颈上皮内瘤变 2/3（CIN2/3）方面有效、安全且耐受性好（Trimble 等人，2020）。I 期临床试验评估了青蒿琥酯栓剂在治疗 HPV 感染细胞具有细胞毒性作用，同时对健康细胞影响最小（Fang 等人，2023）。青蒿琥酯在体外和体内均对血液系统恶性肿瘤表现出多靶点的抗癌活性。其作用于白血病、多发性骨髓瘤和淋巴瘤细胞的主要机制包括氧化应激反应、抑制增殖和诱导多种类型的细胞死亡（Li 等人，2020；Mancuso 等人，2021b）。 由于青蒿琥酯药物高效且耐受性好，无副作用，在完成各种肿瘤的进一步临床试验后，未来可单独或与标准化疗联合应用于抗肿瘤治疗。

6 Conclusion and perspectives

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Cancer is one of the most important and common public health problems on Earth endangering human health. And its incidence rates continue to rise. As anti-tumor drugs have always been the most common methods for treating cancers, searching for new anti-tumor agents is of great significance (Sekeroglu and Tuncal, 2021; He et al., 2023). The use of herbal products is booming all over the world because of being believed as safer than conventional drugs and free of side effects (Mwankuna et al., 2023). Chinese herbal medicine (CHM) has long been applied in the clinic due to its advantages of low toxicity and polypharmacology (Li et al., 2022). CHM plays a positive role in regulating patients' immune system, which helps cancer patients to fight against cancer itself and finally improves patients' life quality (Wang S. M. et al., 2020). ART, a sesquiterpene lactone endoperoxide isolated from Chinese herbal medicine, displays excellent anti-tumor and anti-inflammatory activity (Lu W. J. et al., 2022; Wang et al., 2022). It is safe, efficacious and well-tolerated anti-malarial (Savargaonkar et al., 2020). ART possesses profound cytotoxic activity against tumor cells (Khanal, 2021), which brings new hope for the treatment of diseases. The combination of ART and other anti-tumor drugs may provide a new idea for the treatment of tumors in the future (Duarte and Vale, 2020). In this paper, the anti-tumor mechanism of artesunate and its corresponding signaling pathway are reviewed, and the anti-tumor mechanism of artesunate in different types of tumors is analyzed and explained. In addition to this, we also provide a separate explanation of the anti-tumor mechanism of artesunate in different types of tumors. It provides a comprehensive reference for further study of the anti-tumor mechanism of artesunate, and is conducive to expanding its clinical application. In conclusion, the efficacy of ART as an anticancer agent has been demonstrated in multiple tumor types. However, the anti-tumor mechanism of ART is not completely clear, so it needs to be further studied to obtain more theoretical support and experimental basis.

癌症是地球上最严重和最常见的公共卫生问题之一，威胁着人类健康。而且其发病率仍在持续上升。由于抗肿瘤药物一直是治疗癌症的最常用方法，因此寻找新的抗肿瘤药物具有重要意义（Sekeroglu 和 Tuncal，2021；He 等人，2023）。由于被认为比传统药物更安全且无副作用，草本产品的使用在全球范围内蓬勃发展（Mwankuna 等人，2023）。中药（CHM）因其低毒性和多效性长期以来被应用于临床（Li 等人，2022）。中药在调节患者免疫系统方面发挥着积极作用，这有助于癌症患者对抗癌症本身，并最终提高患者的生活质量（Wang S. M. 等人，2020）。ART 是一种从中药中分离出的倍半萜内过氧化物，具有优异的抗肿瘤和抗炎活性（Lu W. J. 等人，2022；Wang 等人，2022）。它是一种安全、有效且耐受性良好的抗疟药（Savargaonkar 等人，2020）。青蒿素对肿瘤细胞具有深刻的细胞毒性（Khanal，2021），为疾病治疗带来了新的希望。青蒿素与其他抗肿瘤药物的联合使用可能为未来肿瘤治疗提供新思路（Duarte 和 Vale，2020）。本文综述了青蒿素的抗肿瘤机制及其相应的信号通路，并分析了青蒿素在不同类型肿瘤中的抗肿瘤机制。此外，我们还对青蒿素在不同类型肿瘤中的抗肿瘤机制进行了单独的阐述。这为青蒿素抗肿瘤机制的进一步研究提供了全面的参考，有利于扩大其临床应用。总之，青蒿素作为抗癌药物的疗效已在多种肿瘤类型中得到证实。然而，青蒿素的抗肿瘤机制尚不完全清楚，因此需要进一步研究以获得更多的理论支持和实验依据。

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XF: Conceptualization, Methodology, Software, Visualization, Writing–original draft, Writing–review and editing. YY: Visualization, Methodology, Software, Writing–review and editing. YL: Methodology, Software, Writing–review and editing. YS: Conceptualization, Funding acquisition, Writing–review and editing. BL: Conceptualization, Supervision, Validation, Writing–review and editing.

XF：概念提出、方法论、软件、可视化、初稿撰写、审阅与编辑。YY：可视化、方法论、软件、审阅与编辑。YL：方法论、软件、审阅与编辑。YS：概念提出、资金获取、审阅与编辑。BL：概念提出、监督、验证、审阅与编辑。

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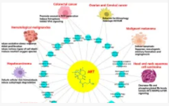
Figures and Tables 图和表

Graphical Abstract 图示摘要



Simran Sinsinwar, Indian Statistical Institute, India

Updates 更新

Check for updates 检查更新

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***Correspondence:** Bo Li, lbo@jlu.edu.cn

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