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REVIEW

Repurposing Artemisinin-Based Drugs from Antimalarial to Pan-Therapeutic: Pharmacological Promise and Therapeutic Challenges

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Abstract: The sourcing of pharmaceutical agents from natural products remains a cornerstone of drug discovery. For millennia, herbal remedies have served as foundational therapeutic interventions, yet their mechanisms of action often remain elusive. Artemisinin (ART, or "Qinghaosu") and its derivatives, collectively known as ARTs, exemplify this paradigm. Originating from traditional Chinese medicine, these well-established antimalarial compounds exhibit potent cytotoxicity, positioning them as promising anti-cancer agents. ARTs operate through multiple cancer cell-intrinsic mechanisms and demonstrate synergistic effects with conventional therapies, even against chemoresistant malignancies. Beyond oncology, the therapeutic portfolio of ART-based drugs is rapidly expanding. This review synthesizes recent advancements in the application of ARTs for treating various cancers, Alzheimer's disease, and reproductive disorders. Furthermore, we explore the frontier of ART drug development, focusing on the rational design of ART-derived molecular hybrids and the engineering of nano-enabled delivery systems. These innovative strategies are pivotal for enhancing anti-cancer efficacy and achieving cancer-specific targeting. Ultimately, this work aims to guide the innovation of ART-based precision medicine, revitalizing the exploration and development of natural products in modern pharmacotherapy.

Keywords: artemisinin, malignancy, neurodegenerative disease, reproductive disorder, drug delivery

Introduction

Naturally occurring substances and medicinal plants constitute a significant reservoir of biologically active compounds that are utilized as potent therapeutic modalities across various diseases.[1–11] Artemisinin (ART) and its derivatives, collectively known as ARTs, are bioactive sesquiterpene lactones extracted from *Artemisia annua*, a traditional herbal medicine with antioxidant and anti-inflammatory properties. ART-based combination therapy has been established as the standard treatment for severe malaria, leading to the awarding of the 2015 Nobel Prize in Medicine to the Chinese scientist Tu You-You for her contributions to the isolation and discovery of ART.

Since the 1970s, several ART derivatives, including dihydroartemisinin (DHA) and artesunate (AS), have been identified, exhibiting enhanced solubility and bioavailability[12] (Figure 1). ARTs have short in vivo half-lives and are capable of diffusing across physiological barriers, such as the blood–brain barrier, which contributes to their advantageous safety and pharmacokinetics in diseases treatment. They contain a tetracyclic core with an endoperoxide bridge (C-O-O-C), which is essential for their cytotoxic properties. Interacting with heme causes the cleavage of the endoperoxide bridge by heme iron (II) oxide, leading to the generation of peroxy free radicals and reactive oxygen species (ROS), which inflict damage on vulnerable biomolecules, including DNA, thereby initiating cell death.

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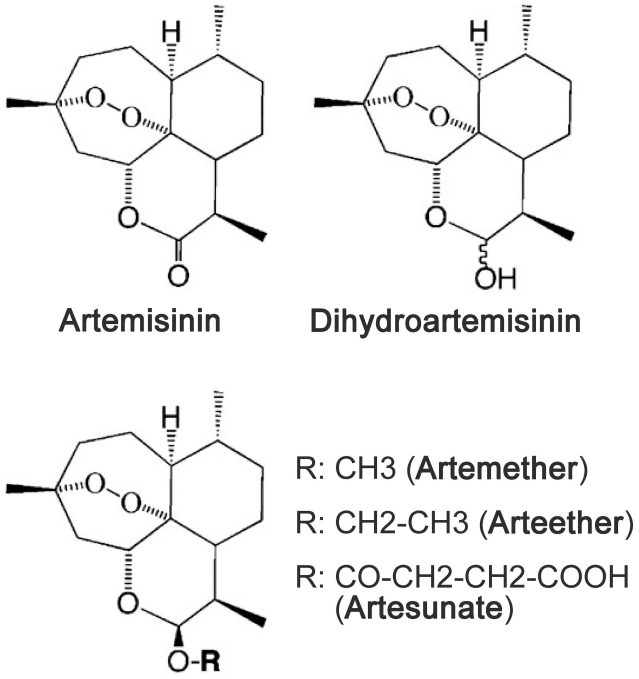

Figure 1 Chemical structure of artemisinin and its derivatives.

ARTs also engage with a diverse array of cellular proteins, thereby participating in multiple biological processes, including apoptosis, autophagy, ferroptosis, glycolysis, and the inflammatory response.[13–18] This endows ARTs with potent pharmacological activities under disease conditions. Compelling evidence suggests that ARTs exhibit selective cytotoxicity toward malignant cells since being first reported in 1993, as most cancer cells express higher levels of transferrin receptors (TfRs) on their surface, featuring an increased influx of iron ions via transferrin mechanism.[16,19–21] Notably, the therapeutic effectiveness even in certain cancers featuring chemoresistance can be significantly improved by the combination of ARTs with chemotherapeutic drugs.

In this review, we provide a comprehensive summary of the recent advancements in the therapeutic properties of ARTs in malignancies, neurodegenerative disorder, and reproductive disease, with an emphasis on their underlying molecular mechanisms and pharmacological effects. We further discuss the recent development of ART-derived hybrids and nanoenabled delivery systems that aim at enhancing the anti-cancer efficacy and cancer-specific targeting property of ARTs, which innovates the ART-based therapeutic applications.

Therapeutic Activities of ARTs in Malignancies

Despite the emergence of chemotherapy in combination with immunotherapy as a promising therapeutic strategy, cancer heterogeneity, along with both primary and acquired resistance to these agents, significantly impedes their efficacy in cancer treatment.[22] ART-based drugs demonstrate anti-cancer effects on various malignancies via multiple mechanisms known to be cancer cell intrinsic. Therefore, the combinatorial treatment with ART-based drugs and other molecular-targeted drugs holds the promise of achieving better outcomes in cancer treatment (Table 1).

The anti-cancer properties of ARTs are primarily attributed to their capacity to induce ferroptosis, a form of programmed iron-dependent cell death induced by overwhelming lipid peroxidation. Ferroptosis functions as a tumor-suppressive mechanism, which is associated with the activities of several tumor suppressors, including p53, BRCA1-associated protein 1 (BAP1), and fumarate hydratase.[47–49] The p53 protein can inhibit ferroptosis through the transcriptional induction of CDKN1A or by interacting with dipeptidyl peptidase 4 (DPP4). Conversely, p53 can promote ferroptosis by transcriptionally repressing the cystine/glutamate antiporter SLC7A11/xCT, which uptakes cysteine for glutathione synthesis.[50] The xCT transporter represents a targetable vulnerability in solid tumors; its deficiency can

Table 1 The Anti-Cancer Therapeutic Effects ARTs on Malignancies

Cancer Type	Drugs	Anti-Cancer Mechanism
Bladder cancer	DHA	Downregulation of KDM3A and p21 expression[23]
Breast cancer	ATA, DHA	Inducing cellular iron deprivation through a transferrin mechanism;[20] Suppressing cancer aggressiveness through inactivation of the TGF-β1/Smads signaling pathway;[24] Reducing angiogenesis through downregulation of VEGF and HIF-1α, as well as Notch signaling pathway;[25] Inhibiting mitochondrial biogenesis through attenuation of CREB/PGC-1α signaling axis[26]
Cervical cancer	DHA	Upregulating caveolin 1 and MTCH2 expression, as well as promoting their translocation to the nucleus[27]
Colorectal cancer (CRC)	DHA	Promoting apoptosis synergistically with halofuginone through activation of caspase-8/9 in 5-FU-resistant CRC cells;[28] Inducing apoptosis in oxaliplatin-resistant CRC cells through modulation of TERT, CD44, and EGFR[29]
Esophageal cancer (EC)	DHA	Sensitizing cisplatin-resistant cells to cisplatin through inhibition of Shh signaling[30]
Gliomas	DHA	Inducing mitochondrial dysfunction and ER stress to trigger both apoptotic and autophagic cell death;[31] Inducing ferroptosis through downregulation of GPX4 expression in glioblastoma cells[21]
Head and neck squamous cell carcinoma (HNSCC)	DHA	Mitigating cancer aggressiveness through inhibition of JAK2/STAT3 signaling pathway;[32] Suppressing cancer invasion and migration through downregulation of TENM2 via miR-195-5p[116]; Inhibiting proliferation through inactivation of POSTN/YAP/IL6 signaling;[33] Inhibiting epithelial-mesenchymal transition and invasion through the miR-130b-3p/IL-6/STAT3/β-catenin signaling axis;[34] Enhanceing autophagy, which downregulates RALB and USP33 expression, leading to inflammasome inactivation[35]
Leukemia	DHA	Induces apoptosis and differentiation in both AML cells and leukemia xenograft mouse models, through the activation of ROS/Bim pathway and TfR1-mediated Fe^{2+} pathway, respectively;[36] Inhibiting leukemia cell proliferation by suppressing aerobic glycolysis through the downregulation of GLUT1 and PKM2[14]
Liver cancer	DHA	Inducing dissipation of mitochondrial membrane potential, release of cytochrome c, activation of caspases, downregulation of Mcl-1, and Bak-mediated intrinsic apoptosis[37]
Lung cancer	DHA	Enhancing immunogenic cell death through ferroptosis-induced ER stress and DNA damage;[16] Reprogramming intratumoral TAMs into the anti-tumor M1 phenotype through ferroptosis and Akt/mTOR signaling pathway;[38] Reducing chemoresistance through downregulation of CIRBP expression and inhibition of EGFR/NRAS/ERK/MAPK signaling pathway;[39,40] Disrupting aerobic glycolysis through downregulation of GLUT1 expression and inactivation of mTOR signaling pathway;[41] Enhancing the sensitivity to cisplatin Treatment by inducing ZIP14 expression and ferroptosis[42]
Melanoma	DHA	Suppressing STAT3 signaling pathway[43]
Primary effusion lymphoma (PEL)	DHA	Inducing apoptosis and exhibiting synergistic anti-proliferative effects with Dox;[44] Enhancings the susceptibility to natural killer cell-mediated cytolysis[45]
Prostate cancer (PCa)	DHA	Inducing apoptosis in metastatic castration-resistant PCa through modulation of the JARID2/EZH2/miR-7/miR-34a/Axl signaling axis[46]

induce ferroptosis, thereby inhibiting metastasis and enhancing the efficacy of anti-PD1 immunotherapy across various cancer types.[51–54] Either deprivation of cysteine or inhibition of glutathione peroxidase 4 (GPX4)—a critical enzyme for peroxide clearance—has been shown to increase sensitivity of aggressive mesenchymal cancer cells to ferroptosis.[48–50,55] Ferroptosis has been demonstrated to enhance therapeutic efficacy of chemotherapy and immunotherapy.[54,56] The pro-ferroptotic activity of ARTs artemisinins cancer is further by the evidence indicating these compounds significantly alter the expression of iron-related genes.[57] DHA increases the susceptibility to GPX4 inhibition-induced ferroptosis in a set of cancer cells that are otherwise highly resistant to ferroptosis, primarily through regulation of iron homeostasis.[13] Mechanistically, it induces the lysosomal degradation of ferritin, a nano-cage complex responsible for iron storage, via an autophagy-independent mechanism, which elevates cellular levels of free iron. The free iron subsequently stimulates the binding of iron-regulatory proteins (IRPs) to those transcripts containing iron-responsive element (IRE) sequence, thereby creating a positive feedback that further promotes free iron accumulation[13] (Figure 2).

Breast Cancer

In breast cancer, DHA demonstrates anti-cancer properties by inducing cellular iron deprivation through a ROS-independent mechanism.[20] Iron (Fe(III)), when bound to transferrin (Tf), is internalized via transferrin receptor 1 (TfR1)-mediated endocytosis. Within the acidic environment of lysosomes, Fe(III) is released and reduced to Fe(II) by the ferrireductase Steap3, followed by its translocation into the cytosol through the divalent metal transporter 1 (DMT1). DHA not only diminishes the levels of cell-surface TfR1 by promoting its palmitoylation and internalization but also

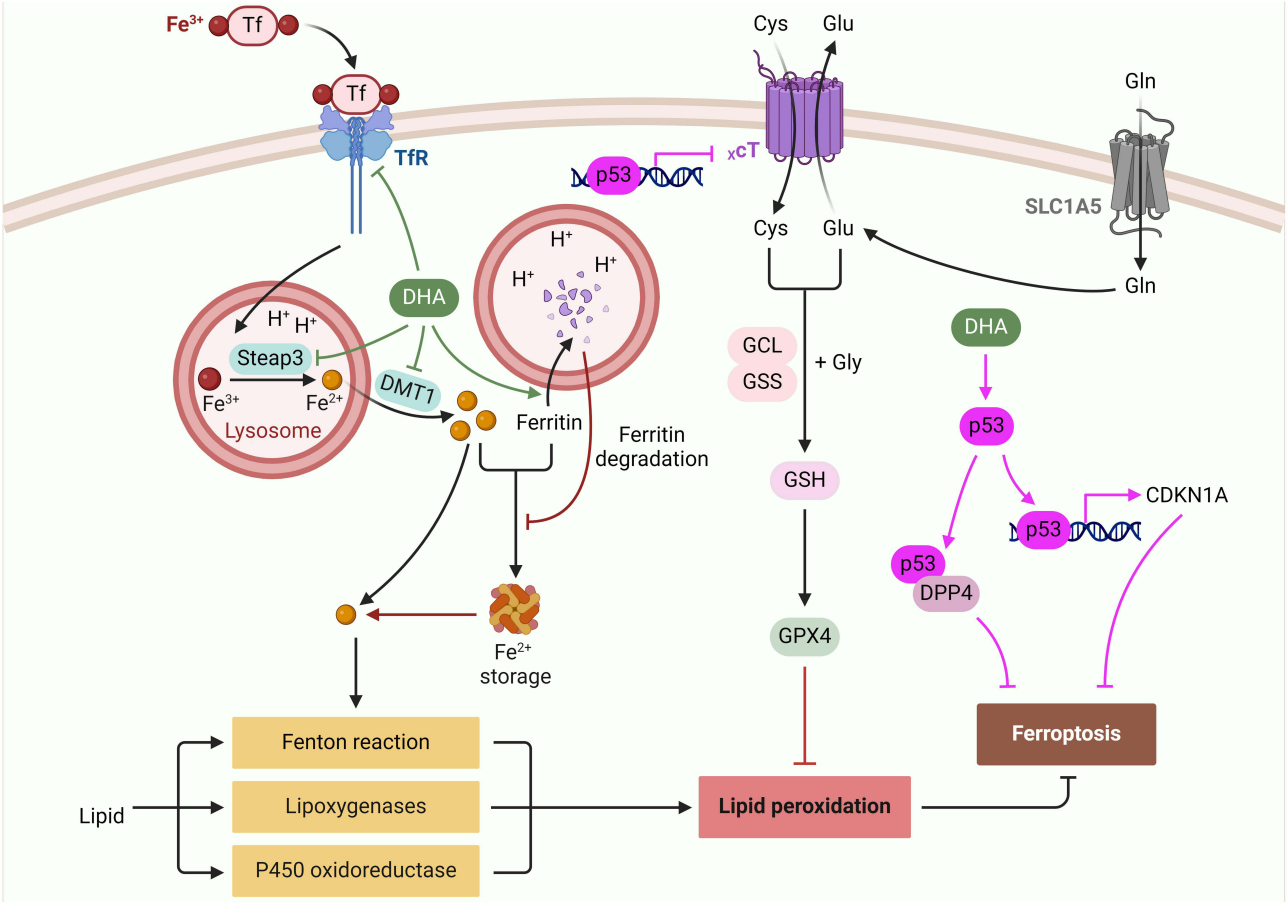

Figure 2 ARTs in modulation of ferroptosis.

down-regulates the expression of Steap3 and DMT1, leading to iron depletion in breast cancer MCF7 cells.[20] Similar phenomena have been observed in hepatocellular carcinoma (HCC) HepG2 cells, suggesting that ARTs may serve as promising candidates for the development of iron-based cancer therapies. Moreover, DHA exhibits more potent anti-breast cancer activity compared to ART, primarily through the inactivation of the TGF-β1/Smads signaling pathway.[24] The TGF-β1-induced aggressiveness of MCF-7 cells is mitigated by DHA treatment. However, the therapeutic application of DHA should be approached with caution due to its potential hepatotoxicity, despite its favorable tolerance observed in the MCF-7 xenograft mouse model.[24]

The anti-breast cancer efficacy of ARTs is also attributable to their ability to inhibit angiogenesis within the tumor microenvironment (TME) (Figure 3). Current Food and Drug Administration (FDA)-approved anti-angiogenic agents primarily target the signaling pathway of vascular growth factor A (VEGFA, also known as VEGF). These agents widely utilized, in combination with immunotherapy and/or chemotherapy for the treatment of various malignancies.[58] In the hypoxic TME, hypoxia-inducible factor 1 (HIF-1), particularly HIF-1α promotes transcription and stabilization VEGF mRNA, thereby enhancing VEGF expression and angiogenesis.[25] ART can reduce the vascular density in tumor tissues and impair the proliferation of breast tumor xenografts in the nude mice, by down-regulating the expression of angiogenesis-related factors VEGF and HIF-1α.[25] Notch signal-related factors Notch1, Delta-like ligand-4 (Dll4), and Jagged ligand-1 (Jag-1), which are known to promote angiogenesis and cancer aggressiveness, are also down-regulated by ART in a breast tumor xenograft mouse model.[25,36,59]

In another study, it is observed that ART enhances the sensitivity of breast cancer cells to the chemotherapeutic agent vinorelbine (NVB), a drug commonly utilized for its anti-angiogenic properties, by inhibiting mitochondrial biogenesis.[26] Mitochondrial metabolism plays a crucial role in angiogenesis and tumor progression, which is stimulated by VEFG and

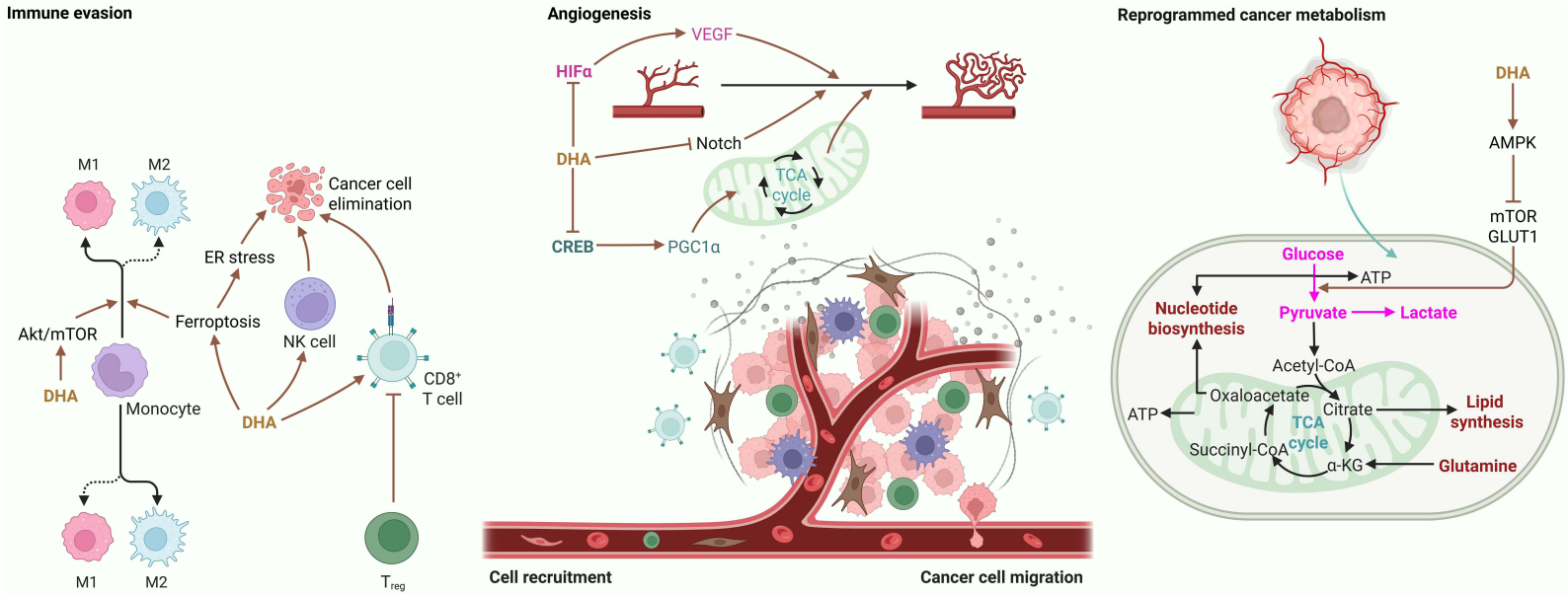

Figure 3 ARTs induce the reprogramming of TME to exhibit anti-cancer efficacy. Note that the immune evasion in TME is featured by: 1) low immunogenicity of cancer cells; 2) polarization of TAM into pro-tumor M1 type; 3) insufficient infiltration of cytotoxic T cells; and 4) recruitment of pro-tumorigenic regulatory T (Treg) cells and pre-mature dendritic cells.

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peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α).[60–64] Both VEGF and PGC-1α are subject to regulation by the cAMP response element-binding protein (CREB), which is notably overexpressed in various malignancies, including mesothelioma, breast cancer, and lung cancer.[26,65] The combination of ART and NVB significantly inhibits tumor growth by targeting the CREB/PGC-1α signaling axis in a breast tumor xenograft mouse model.[26]

Cervical Cancer

In cervical cancer, DHA induces anti-cancer effects by upregulating caveolin 1 (Cav1) and mitochondrial carrier homolog 2 (MTCH2), as well as promoting their translocation to the nucleus.[27] Cav1 contributes to p53 activation by facilitating its nuclear localization and stabilization; furthermore, the loss of Cav1 has been linked to tumorigenesis across various cancer types.[27,66] In addition, MTCH2 contributes to apoptosis through its direct interaction with and recruitment of truncated Bid (t-Bid).[67] Cav1 also negatively regulates antioxidant signaling by directly interacting with and inhibiting nuclear factor erythroid 2-related factor 2 (Nrf2).[68] Consequently, the sensitivity of cervical cancer cells to DHA can be augmented by the overexpression of Cav1 and MTCH2. This study indicates that DHA functions as a p53 activator, thereby inhibiting cancer cell viability.[27]

Lung Cancer

Lung cancer stands as one of the three malignancies with the most unfavorable prognosis.[69] ARTs exhibit anti-lung cancer activity also by enhancing anti-tumor immunity within the TME (Figure 3). The immunosuppressive nature of TME is characterized by the low immunogenicity of cancer cells, the insufficient infiltration of cytotoxic T cells, the high abundance of regulatory T cells, and the predominance of immature dendritic cells and pro-tumor M2-type tumor-associated macrophages (TAMs). These factors compromises the effectiveness and safety of anti-cancer immunotherapy.[70–72] DHA is shown to exhibit promotive effects on immunogenic cell death through ferroptosis-induced endoplasmic reticulum stress and DNA damage, thereby reshaping the TME for renovation of anti-cancer immunity in lung cancer while exhibiting low toxicity to normal cells.[16,73,74] It also induces ferroptosis in TAMs, which causes DNA damage and NF-κB activation, leading to phenotypic remodeling of intratumoral TAMs into the anti-tumor M1 phenotype.[38] The immunogenicity-promoting activities of DHA can be subverted by ferroptosis inhibition while it is enhanced by exogenous iron ions, which is reminiscent of the finding that higher levels of ions are observed in malignant cells, including lung cancer cells.[16,38,75] DHA has also been proposed as an M1 stimulus through the Akt/mTOR signaling pathway in a Lewis lung carcinoma (LLC) model. Additionally, DHA enhances the proinflammatory response and phagocytic capacity in TAMs, and the M1-related phenotypes induced by DHA can be inhibited through the blockade of mTOR signaling.[15]

The NRAS gene, an oncogene of the N-Ras family, exhibits significantly elevated expression levels in lung cancer. Mutations in NRAS lead to malignant proliferation via the ERK/MAPK signaling axis and inhibit DNA damage response, thereby contributing to chemoresistance in various cancers.[39,76–79] Recent studies have indicated that ARTs possess anti-lung cancer potency by acting as direct inhibitors of epidermal growth factor receptor (EGFR), thereby impeding the NRAS/ERK/MAPK signaling pathway. This finding aligns with previous reports suggesting that DHA is more effective in cancers harboring mutations in EGFR or NRAS.[39,80]

Patients with non-small cell lung cancer (NSCLC) have only 26% of 5-year survival rate.[81] NSCLC cells feature high propensity of developing radioresistance following fractional radiation (2 Gy per day for consecutive 20 days). DHA can reduce the radiation-induced mitophagy and radioresistance of NSCLC via inhibition of cold-inducible RNA binding protein (CIRBP) which shows highly expression in radioresistant NSCLC.[40] DHA also induces apoptosis in NSCLC cells by disrupting aerobic glycolysis, primarily through the inactivation of mechanistic target of rapamycin (mTOR) and downregulation of glucose transporter GLUT1. Reactivation mTOR or overexpression GLUT1 significantly mitigates DHA-induced apoptosis in NSCLC cells by restoring glycolytic metabolism that is attenuated by DHA. Notably, DHA exhibits a synergistic effect with the glycolytic inhibitor 2-Deoxy-D-glucose (2DG) by activating caspases-3, −8, and −9, as well as promoting the release of cytochrome c, thereby enhancing apoptosis in NSCLC cells while demonstrating no significant toxicity to normal lung fibroblast cells.[41,82]

Liver Cancer

Liver cancer is a common malignancy characterized by rapid progression, early recurrence, and poor prognosis.[83] DHA induces the dissipation of mitochondrial membrane potential (ΔΨm), release of cytochrome c, activation of caspases, downregulation of Mcl-1, and Bak-mediated intrinsic apoptosis in hepatocarcinoma (HCC) cells. These phenomena can be diminished by Bax deficiency and enhanced by Mcl-1 deficiency.[37] Although the expression of Puma and Noxa remains unchanged following DHA treatment, apoptosis induced by DHA is suppressed when Puma, Noxa, or Bim is silenced.[37] Furthermore, artesunate and DHA exhibit a synergistic effect with the heat shock protein 70 (HSP70) inhibitor VER-155,008 to induce apoptosis in HCC cells.[84] HSPs, frequently overexpressed in human cancers, are essential for maintaining cellular homeostasis.[85] HSP70 subfamily includes the constitutively expressed heat shock cognate 70 kDa protein (HSC70), the heat shock-inducible HSP70, and the glucose-regulated 78 kDa protein (GRP78). HSC70 involves in the tumorigenesis-promoting autophagy and GRP78 modulates unfolded protein response for tumorigenesis, while HSP70, with significant upregulation in HCC, drives tumor aggressiveness and chemotherapy resistance.[84–88]

Wang et al (2024) have identified rhein, an active compound derived from *Rheum undulatum L*., as a novel HSP70 inhibitor that enhances the sensitivity of HCC cells to artesunate or DHA.[89] Importantly, rhein also suppresses CRC by inactivating the mTOR signaling, inhibits nasopharyngeal carcinoma by inducing Ca^{2+}-dependent mitochondrial death signaling, and inhibits renal cell carcinoma by attenuating MAPK/NF-κB signaling.[90–92] mTOR complex 1 (mTORC1) is known to promote the biosynthesis of macromolecules required for cellular growth and homeostasis.[93] DHA activates AMP-activated protein kinase (AMPK) for mTORC1 inhibition, thereby impairing the proliferation and viability of rhabdomyosarcoma cells but not normal cells. These inhibitory effects can be mimiced by artesunate and be diminished by both genetic and pharmacological inhibition of AMPK.[94]

Colorectal Cancer

Colorectal cancer (CRC) ranks as the second leading cause of cancer-related mortality globally. The primary chemotherapeutic agent employed in CRC treatment is 5-Fluorouracil (5-FU); however, the sensitivity of CRC cells to 5-FU is diminished by p53 knockout.[95] The tumor suppressor p53, which is encoded by the TP53 gene, functions as a transcription factor with over 4000 binding sites within the human genome.[96] Loss-of-function mutations in TP53 are frequently observed across various malignancies, including breast cancer and CRC, and are correlated with unfavorable prognoses and chemoresistance.[97,98] Yao et al (2018) demonstrate that DHA effectively restores 5-FU sensitivity in TP53-deficient CRC cells.[95] Furthermore, Gong et al (2022) report a synergistic effect between ART and halofuginone (HF), a bioactive compound derived from the traditional Chinese herb *Dichroa febrifuga Lour* (*Changshan* in Chinese), in promoting caspase-dependent apoptosis via activation of caspase-8/9 in 5-FU-resistant CRC cells, both in vitro and in vivo.[28,99] Interestingly, ART alone activates only caspase-9; however, when caspase-9 is inhibited, ART activates caspase-8 via induction of autophagy. In this scenario, with defective apoptosis, CRC cells switch to autophagic cell death in response to combination treatment with ART and HF.[28] β-Lapachone (β-Lap), a NAD(P)H:quinone oxidoreductase 1 (NQO1) bioactive phytochemical derived from the lapacho tree, induces NQO1-mediated tumour-specific cell necrosis and has been tested in clinical trials for the treatment of solid tumors.[100–102] The polyphenols extracted from Korean *Artemisia annua L*. potentiates the anti-cancer efficacy of β-lapachone in both parental and oxaliplatin-resistant CRC cells by inducing DNA damage and apoptosis through modulation of telomerase reverse transcriptase (TERT), CD44, and EGFR.[29]

Gliomas

Gliomas are the primary brain tumours originating from neural stem or progenitor cells that harbor tumour-initiating genetic alterations.[103] DHA is reported to exert anti-glioblastoma activity by inducing mitochondrial dysfunction and endoplasmic reticulum (ER) stress, leading to both apoptotic and autophagic cell death in human glioblastoma cells.[31] Compared to normal astrocytes, glioblastoma cells feature an elevated expression of TfR, a type II transmembrane protein involved in iron uptake, and the associated elevation in cellular iron levels contributes to DHA-induced

ferroptosis in glioblastoma.[21] Despite with constant expression of SLC7A11/xCT and acyl-CoA synthetase long-chain family member 4 (ACSL4), the expression of GPX4 in glioblastoma cells is significantly decreased by DHA.[21] Of note, ACSL4 is an executor of ferroptosis with preferential expression in basal-like breast cancer cells and dictates ferroptosis sensitivity by shaping cellular lipid composition.[104] While with ferroptosis-inducing activity, DHA is reported to initiate the HSP family A member 5 (HSPA5)-mediated ferroptosis inhibition in glioma cells.[105] HSPA5 is an ER chaperone involved in lipid metabolism. DHA-induced unfolded protein response in the ER upregulates HSPA5 expression via the protein kinase R-like ER kinase (PERK)-activating transcription factor 4 (ATF4) signaling pathway, which thereby increases the expression and activity of GPX4, protecting glioma cells from ferroptosis. Genetic and pharmacological inhibition of PERK-ATF4-HSPA5-GPX4 pathway enhances the susceptibility of glioma cells to DHA-induced ferroptosis.[105]

A recent genome-wide screening revealed that porphyrin (heme) biosynthesis is essential for the cytotoxicity of DHA in eukaryotic cells.[106] Pharmacological inhibition of porphyrin biosynthesis significantly decreases susceptibility to DHA, while pharmacological activation of porphyrin biosynthesis produces the opposite effect. 5-Aminolevulinic acid (5-ALA), a clinically approved enhancer of porphyrin synthesis, sensitizes multidrug-resistant, patient-derived high-grade gliomas to DHA. Furthermore, a combinatorial treatment involving 5-ALA and artesunate demonstrates a potent synergistic anticancer effect in reducing glioblastoma growth in patient-derived xenograft mouse models.[106] This study thus identifies a novel combination therapy for human cancers, including drug-resistant glioblastomas.

Hematologic Cancer

In primary effusion lymphoma (PEL), a rare and aggressive B-cell lymphoma for which effective therapies are lacking, DHA has been shown to induce apoptotic cell death and importantly, it exhibits synergistic anti-proliferative effects when combined with the chemotherapeutic agent doxorubicin.[44] Additionally, ART enhances the susceptibility of cancer cells to natural killer (NK) cell-mediated cytolysis. NK cells serve as the sentinel of tumor surveillance, and immunotherapy targeting NK cells has demonstrated significant anti-cancer efficacy.[45,107,108] Interestingly, ART does not induce apoptosis in hematopoietic cancer cells; rather, it sensitizes these cells to apoptosis in the context of NK cell cytolysis, while preserving both the tumor recognition capabilities and the overall architecture of NK cells.[45]

Leukemia encompasses a group of aggressive hematopoietic malignancies that are characterized by genetic alterations and chromosomal abnormalities affecting the proliferation and differentiation of hematopoietic stem and precursor cells (HSPCs).[109] Acute myeloid leukemia (AML) is specifically marked by the accumulation of undifferentiated myeloid blasts. Although numerous anti-AML therapies are available, particularly the differentiation therapies utilizing all-trans retinoic acid and arsenic trioxide, the prognosis for most other subtypes of AML remains unfavorable.[110–114] Artesunate has been proposed as a novel chemotherapeutic agent for AML, as it induces apoptosis and differentiation in both AML cells and leukemia xenograft mouse models, while exhibiting minimal cytotoxicity towards healthy HSPCs, bone marrow mononuclear cells, and experimental animals.[36] The apoptosis induced by artesunate is associated with the activation of ROS/Bim pathway, whereas the TfR1-mediated Fe^{2+} pathway constitutes a mechanism of artesunate-induced differentiation.[36] Furthermore, DHA has been demonstrated to inhibit leukemia cell proliferation by suppressing aerobic glycolysis through the downregulation of GLUT1 and pyruvate kinase M2 (PKM2).[14]

Prostate Cancer

Prostate cancer (PCa) is the most prevalent solid malignancy among aging males. Although effective therapeutic strategies exist for local PCa, such as androgen ablation therapy, there are limited pharmacological options available for hormone-refractory metastatic PCa.[115] The receptor tyrosine kinase Axl is frequently upregulated in various malignancies, including prostate and breast cancers, and is associated with poor overall survival rates and increased chemoresistance.[116–120] Axl expression in PCa has been found to be inversely correlated with the expression levels of miR-7 and miR-34a.[46] DHA demonstrates its anti-cancer effects on metastatic castration-resistant PCa by targeting the Jumonji, AT-rich interaction domain containing 2 (JARID2)/enhancer of zeste homolog 2 (EZH2)-miR-7/miR-34a-Axl signaling axis, which leads to apoptosis of PCa cells and inhibition of tumor growth. Mechanistically, DHA down-regulates JARID2 and EZH2, both components of the polycomb repressive complex 2 (PRC2), which subsequently leads

to the upregulation of miR-7 and miR-34a, thereby inhibiting Axl translation. Notably, DHA has been shown to synergize with docetaxel to enhance the survival rate of PCa xenograft mice.[46] Furthermore, by activating the EGFR/PKC/mTOR signaling axis, Axl confers the chemoresistance to PI3Kα inhibition in head and neck squamous cell carcinoma (HNSCC) and esophageal squamous cell carcinoma (ESCC).[120]

Head and Neck Cancer

HNSCC is the primary form of head and neck cancer and is associated with a poor prognosis, ranking seventh in global cancer prevalence.[121] DHA has been shown to mitigate the aggressiveness of HNSCC by inhibiting Janus Kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway.[32] Notably, suppression of STAT3 signaling pathway also underlies the mechanism by which DHA inhibits the proliferation, migration, and pulmonary metastases of melanoma.[43] Recent findings indicate that DHA can suppress HNSCC invasion and migration through the downregulation of TENM2 via miR-195-5p.[122] DHA also exhibits anti-proliferative and pro-apoptotic effects on laryngeal squamous cell carcinoma (LSCC), a type of HNSCC, by inactivation of periostin (POSTN)/Yes-associated protein (YAP)/IL-6 signaling which is implicated in the tumorigenesis of various malignancies, including CRC.[33,123,124] Additionally, DHA inhibits epithelial–mesenchymal transition (EMT) and LSCC invasion via the miR-130b-3p/IL-6/STAT3/β-catenin signaling axis.[34]

In laryngeal squamous cell carcinoma (LSCC), the tumor-suppressive effects of DHA is mediated through the inhibition of inflammasome.[35] The smoldering inflammatory TME constitutes an incubator for the progression and therapy resistance in nearly all cancer types.[125] Inflammasome activates caspase-1 and promotes the production of pro-inflammatory cytokines interleukin (IL)-1β and IL-18. It is shown that a lower expression of the inflammasome component absent in melanoma 2 (AIM2), a PYHIN protein, is associated with a poorer survival rate in patients with hypopharyngeal squamous cell carcinoma (HSCC); while the overexpression of interferon gamma inducible protein 16 (IFI16), another PYHIN protein, is positively correlated with caspase-1-mediated pyroptosis in LSCC.[35,126,127] DHA enhances autophagy, which downregulates the expression of RAS like proto-oncogene B (RALB) and ubiquitin-specific protease 33 (USP33), leading to the inactivation of IFI16/caspase-1 inflammasome. Consequently, IL-1β production in the serum and TME is compromised in Hep-2 xenograft mouse model.[35]

Esophageal Cancer

Esophageal cancer (EC) is one of the most lethal cancers and its mortality rate ranks among the top ten in China. DHA has been shown to induce an autophagy-dependent cell cycle arrest in esophageal cancer Eca109 cells.[123] A common subtype of EC is ESCC—one of the most incurable malignancies due to the prevalence of drug resistance.[128] Hyperactivation of sonic hedgehog (Shh) signaling is a contributing factor to carcinogenesis, cancer stemness maintenance, and chemoresistance, and is associated with poor outcomes in ESCC patients undergoing platinum-based chemotherapy,[30,129–131] Importantly, continuous chemotherapy with cisplatin can activate Shh signaling to enhance the cancer stem cell-like phenotype of ESCC cells. By acting as an inhibitor of Shh signaling, DHA attenuates the cisplatin-activated Shh signaling and sensitizes cisplatin-resistant ESCC to cisplatin.[30] Notably, by inducing ZIP14 expression and ferroptosis, DHA also enhances cisplatin sensitivity in lung cancer, which may optimize the treatment outcomes of lung cancer chemotherapy[42] (Figure 4).

Clinical Trials on ARTs in Cancer

Despite the well-documented anti-cancer effects of ARTs in basic research, only a limited number of compounds have progressed to clinical trials. In 2011, Jansen et al conducted a pilot study to investigate the clinical benefits, safety, and tumor marker effects of the orally administered ART derivative, Artenimol-R, in patients with advanced cervical cancer. The study observed that, following a 28-day treatment period, clinical remission was achieved, with a median time for the disappearance of symptoms being 7 days. Importantly, no adverse events of grades 3 or 4 were reported, suggesting an improvement in clinical symptoms and good tolerability of Artenimol-R in patients with advanced cervical cancer.[132]

In 2014, Ericsson et al conducted an investigation into the pharmacokinetics of AS and DHA following long-term oral administration of AS in a cohort of 23 patients with metastatic breast cancer. The study demonstrated that the

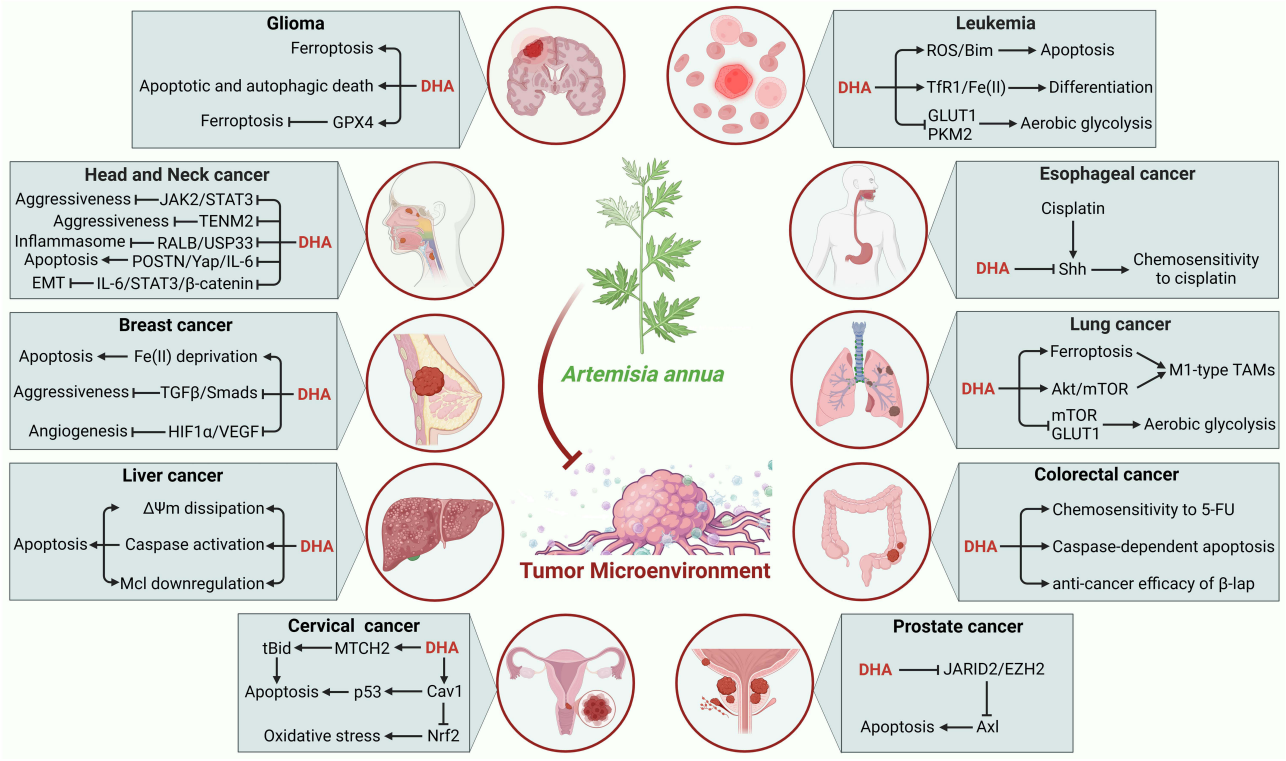

Figure 4 Representative therapeutic mechanisms of ARTs in various malignancies.

population pharmacokinetics of AS and DHA can be accurately characterized by a combined drug-metabolite model without any covariates, alongside a significant increase in the elimination rate of DHA over time. Furthermore, the estimated saliva/plasma ratio of DHA aligns closely with the reported unbound fraction of DHA in human plasma, while the concentrations of AS in saliva exhibit a poor correlation with plasma concentrations.[133]

In 2014, Krishna et al investigated the anticancer activity of AS in a cohort of 23 CRC patients. Following a 14-day regimen of oral administration of 200 mg AS, Bayesian analysis indicated a probability of 0.89 for a reduction in Ki67 expression and 0.79 for an increase in CD31 expression, and no death reported in AS group, in contrast to three deaths in the placebo group. Furthermore, the relapse-free survival rate following AS treatment was significantly higher than that of the placebo group (0.89 vs 0.5 at 42 months), suggesting that AS possesses anti-CRC activity with a favorable tolerability.[134]

In 2016, König et al investigated the safety and tolerability of a four-week AS therapy in patients with breast cancer. They showed that daily doses of 100 mg, 150 mg, and 200 mg were well tolerated among individuals with metastatic or locally advanced breast cancer. Furthermore, it was observed that any dose-limiting adverse events (DL-AEs) were completely reversible after the therapy.[135]

In 2017, von Hagens et al recruited 23 patients with metastatic breast cancer and divided them into three groups based on the administration of oral AS at doses of 100 mg/day, 150 mg/day, and 200 mg/day, with the objective of defining the well-tolerated dose for use as add-on therapy. Throughout the trial period of 4 ± 1 weeks, three patients experienced a total of six DL-AEs, suggesting that an oral dose of up to 200 mg/day is both safe and well tolerated.[136] In a subsequent follow-up study, 25 AEs grade ≥ 2 and at least possibly related to long-term AS therapy were documented, with the distribution of events being 2, 6, and 17 across the 100 mg, 150 mg, and 200 mg/day dose groups, respectively. Thus, they concluded that long-term administration of oral AS at doses of up to 200 mg/day over a cumulative treatment duration of 1115 days does not present significant safety concerns for patients with metastatic breast cancer.[137]

In 2018, Deeken et al conducted a Phase I trial to explore the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of intravenous AS in 19 patients with advanced solid malignancies. The administration of intravenous

AS was performed on the first and eighth days of a 21-day cycle. The results indicated that DLTs were observed at doses of 12, 18, and 25 mg/kg, while the MTD was determined to be 18 mg/kg.[138]

ART-Based Hybrid Entity

Efforts that improve the therapeutic effectiveness of ARTs have led to the discovery of ART-derived hybrid entities that exhibit more favorable druggability. Compared to native pharmacophore, ART hybrids posses many advantages, including enhanced therapeutic activity, improved pharmacokinetic profile, less cross-resistance, and reduced side effects[139–141] (Table 2).

ART with piperazine-containing groups at 10-position carbon (C10) exhibit improved inhibitory effects on hepatocellular cancer cells, while introducing fluorine atoms into piperazine-containing groups to ART improves its anti-cancer activity in multidrug-resistant breast cancer cells, pheochromocytoma cells, and CRC cells.[142,143] The six-membered cyclic carbamate ART derivatives containing piperazine and fluorine groups show excellent anti-cancer effects compared to ART and DHA, with lower cytotoxicity in normal liver cells than Dox. Among them, compound 12h exhibits potent anti-cancer activities in CRC cells but not in glioblastoma cells and lung adenocarcinoma cells, via a mechanism of mitochondria-mediated pathway.[143] These findings envision further endeavors to develop novel ART-based entities with less side effects and improved disease-mitigating activities.

Incorporating the pharmacophore of melphalan into the basic scaffold of ART with a succinic linker lead to the discovery of a compound ARS4 that exerts excellent anti-proliferative and pro-apoptosis activities in ovarian cancer while with low cytotoxicity to normal cells. Further structure optimization produces multiple ARS4 derivatives exhibiting cytotoxicity potency against liver and ovarian cancer models.[144] A series of synthesized 1,3,4-oxadiazole-ART hybrids also show more potent anti-proliferative activities against five human cancer cell lines than ART and 5-FU. Among them the A8 compound induces ferroptosis and apoptosis in breast cancer MCF-7 cells.[145] In another study, a series of bile acid-ART hybrids show promising anti-leukemic effects against both sensitive and multidrug-resistant cells, with amide hybrid 25 being the most active compound that is more potent than the chemotherapeutic drug doxorubicin (Dox).[146]

DHA in conjugation with multiarm polyethylene glycol shows improved blood circulation half-time, water-solubility, and cancer-inhibitory effect of native DHA, while the hybrid of DHA-5-methylisatin tethered by two-carbon linker exhibits profound cytotoxicity potency against both drug-sensitive and drug-resistant breast cancer cells.[147,148] A hybrid of clinically established agents sulfasalazine (SAS) and DHA, termed AC254, demonstrates potentiated chemotherapeutic efficacy in human glioma cells when compared to the combination treatment of native SAS and DHA, with a minor cytotoxicity towards primary neurons and astrocytes.[149]

Table 2 ART-Based Hybrid Entities Exhibit Improved Therapeutic Effectiveness

ART-Based Hybrid	Key Feature and Main Outcome
ART with piperazine-containing groups	Improved inhibitory effects on HCC and CRC through a mechanism of mitochondria-mediated pathway[142,143]
ART-melphalan	Excellent anti-proliferative and pro-apoptosis activities in ovarian cancer[144]
ART-1,3,4-oxadiazole	More potent anti-proliferative activity than ART and 5-FU, inducing ferroptosis and apoptosis in breast cancer[145]
ART-bile acid	More potent anti-leukemic effects against both sensitive and multidrug-resistant cells than Dox[146]
DHA-polyethylene glycol	Improved blood circulation half-time, water-solubility, and cancer-inhibitory effect[147]
DHA-5-methylisatin	Profound cytotoxicity potency against both drug-sensitive and drug-resistant breast cancer[148]
DHA-sulfasalazine	Potentiated anti-cancer efficacy in glioma when compared to the combination treatment of SAS and DHA[149]
ART-nitrogen mustard	Inducing genotoxic stress and apoptosis in leukemia cells, with lower side effect toxicity than chlorambucil and Dox; Impeding leukemia cell proliferation by disruption of cellular redox homeostasis[150]
Ring-contracted ART dimers	Improved anti-proliferative effects over ART on pheochromocytoma cells[48]
DHA-N-Alkyl triphenylvinylpyridinium	A preferential delivery of DHA to the mitochondria of cancer cells; Inducing cell cycle arrest, through the inactivation of mTOR and ERK1/2 signaling pathways, and disrupting mitochondrial metabolism in human melanoma and pancreatic cancer cells[151]
DHA- triphenylphosphonium	Selectively triggering mitochondrial oxidative stress and ER stress and acting as a potent inducer of Immunogenic cell death in breast cancer[152]

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Nitrogen mustard derivatives, chlorambucil, melphalan, and cyclophosphamide, are extensively used DNA-alkylating agents in cancer chemotherapy.[153] Synthesis of nitrogen mustard-ART hybrids obtains a lead compound 5a that effectively causes DNA damage-mediated genotoxic stress and Bcl2 downregulation-mediated apoptosis in leukemia cells, with lower toxicity towards normal liver cells than chlorambucil and Dox.[150] 5a also hinders leukemia cell proliferation by disrupting cellular redox signaling, due to the activation of glutathione peroxidase (GPx) which catalyzes the peroxidation of glutathione (GSH) to deplete ROS.[150,154] In addition, the ring-contracted ART dimers linked by a phosphate ester moiety exhibit improved anti-proliferative effects over ART, with compound 8b shows prominent anti-cancer activity in pheochromocytoma cells, via inducing arrested cell cycle and caspased-dependent apoptosis.[48]

Given the significant difference of mitochondria inner membrane potential in cancer cells compared to normal cells, conjugating DHA with N-Alkyl triphenylvinylpyridinium (TPVP), a mitochondria-accumulating agent, leads to a preferential delivery of DHA to the mitochondria of cancer versus normal cells.[151,155] TPVP-DHA induces G1 cell cycle arrest, via the inactivation of mTOR and ERK1/2 signaling pathways, and disrupt mitochondrial metabolism, in human melanoma and pancreatic cancer cells in a dose-dependent way.[151] Conjugating triphenylphosphonium (TPP) to DHA leads to the development of a mitochondria-targeting DHA (TPP-DHA) that selectively triggers mitochondrial oxidative stress and ER stress, thus acting as a potent inducer of Immunogenic cell death (ICD).[152] ICD occurs in stressed or dying cells and triggers anti-cancer immunity by the release of damage-associated molecular patterns (DAMPs), including calreticulin (CRT) which acts as "eat-me" signals to facilitate the phagocytosis of dendritic cells (DCs), ATP which acts as "find me" signal for recruiting DCs to sites of ICD, and high-mobility group box 1 (HMGB1) which is liberated to the extracellular environment that enhances DCs' antigen presentation effect.[156,157] TPP-DHA-treated cancer cell vaccine effectively establishes an immunogenic TME, which strengthens the efficacy of anti-breast cancer.[152]

Nano-Enabled Delivery System

Since ARTs exert cytotoxicity against both normal cells and cancer cells via ROS-mediated DNA damage, their side effects on normal cells cannot be ignored. Thus, the effectiveness of ARTs in cancer therapy could be improved by site-specific drug delivery as well as the synergistic effects of extra components. Nanoenabled delivery system, including liposome and nanoparticle, enables an active and passive drug release strategy that offer enhanced permeability, prolonged retation, and site-specific accumulation of drugs for disease treatment[158–160161](Table 3).

DHA loaded 2-monoacylglycerol mimetic liposomes promote DHA accumulation in mesenteric lymphatic nodes, significantly improving its oral bioavailability through intestinal lymphatic transport.[162] Kang et al design a mannosylated LNP composed of soybean phospholipids (SPC), cholesterol, and DSPE-PEG2000-mannose (referred to as Man-lip) for the co-delivery of DHA and Dox in multidrug-resistant colon cancer.[164] This Man-lip demonstrates effective endocytosis by drug-resistant human colon cancer HCT8/ADR cells, which exhibit overexpression of the mannose receptor CD206. In comparison to treatments involving Dox alone or the combination of DHA and Dox, Man-lip exhibits enhanced tumor-targeting drug delivery and increases the nuclear accumulation of Dox, leading to both apoptotic and autophagic cell death in drug-resistant colon cancer cells.[164] Zhao et al introduce a self-targeting biomineralized apoferritin-based nano-platform (Ca/DHA@AFn) that leverages calcicoptosis and ferroptosis dual therapy, circumventing the insufficient intracellular ROS and sub-optimal drug accumulation within breast cancer, which hinders the efficacy of ferroptosis. Ca/DHA@AFn demonstrates a uniform distribution and high biocompatibility, exerting synergistic anti-cancer effects when compared to single-modality treatments, which thereby extends the survival rate of mice bearing breast cancer.[172]

Glycolysis Inhibition

Cancer cells engage active metabolic rewiring, with a preference for aerobic glycolysis (also known as the Warburg effect), to create a conducive microenvironment for their maximal survival.[176] The observed upregulation in GLUTs in cancer cells is correlated with cancer aggressiveness, making GLUTs attractive targets of starvation therapy for cancer treatment.[177] By encapsulating DHA, 2,20-azobis [2-(2-imidazolin-2-yl) propane] dihydrochloride (AI), and Ink into the sodium alginate hydrogel, Su et al develop a low-temperature photothermal-induced alkyl radical ((R•)) release system

Table 3 A Summary of the Representative Nana-Enabled Drug Delivery System

Carrier Materials	Cargo	Main Outcomes
DHA dimeric nanoparticle bridged with disulfide bond	DHA	An redox-responsive nanoprodrug for the release of DHA under stimulation by TME triggers GSH and H_2O_2, demonstrating anti-cancer activity in HCC via mitochondrial apoptosis pathway[143]
2-monoacylglycerol liposome	DHA	Improved oral bioavailability through intestinal lymphatic transport[162]
Soybean phospholipids, DOPE, DOPC, RGS peptide	DHA, chloroquine (CQ)	A pH/ROS dual-responsive liposome with fusogenic properties to escape from the acidic lysosomal environments that enables co-delivery of DHA and CQ to the cancers that overexpress αvβ3 integrin, thereby inhibiting angiogenesis via downregulation of VEGF expression and reducing metastasis via maintenance of the attachment between cancer cells and extracellular matrix[163]
Soybean phospholipids, cholesterol, DSPE-PEG2000-mannose	DHA and Dox	Enhanced tumor-targeting co-delivery of DHA and Dox and increased nuclear accumulation of Dox, leading to both apoptotic and autophagic cell death in multidrug-resistant colon cancer[164]
4-Arm-PEG	DHA, DTX	A pH-sensitive system that allows co-delivery of DHA and DTX preferentially to the TME, potently inhibiting the aggressiveness of metastatic breast cancer, through downregulation of Akt, NF-κB and MMP-2 expression[158]
$mPEG_{113}$-b-P(DPA_{60}) copolymer	ART	A pH/ROS dual-responsive system that enables a preferential tumoral accumulation of DHA and RSL-3, suppressing PDAC aggressiveness in both immune-deficient and iimmune-competent mouse models[165]
2,20-azobis [2-(2-imidazolin-2-yl) propane] dihydrochloride, Ink, sodium alginate hydrogel	DHA	A low-temperature photothermal-induced alkyl radical release system that exacerbates mitochondrial damage and energy exhaustion in HCC[166]
Polyglutamic acid, polyethylenimine	DHA, Mitoxantrone	A pH and ROS dual-responsive autocatalytic release system that potentiates CRC immunotherapy and, when combined with PD-1 blockade immunotherapy, significantly inhibits tumor growth and improves the survival of CRC-bearing mice[167]
Transferrin, L-buthionine-sulfoximine, CellROX	DHA	An acidic pH-responsive liposome enables cancer-specific drug delivery via Tf-TfR binding and TfR-mediated endocytosis, which releases Fe(II), DHA, and BSO, achieving amplification of oxidative stress-mediated HCC theranostics[168]
Magnetic nanoparticle (MNP)	ART/DHA/AS	The pH-responsive MNP enables a synergetic CDT and ferroptosis therapy, exhibiting significant anti-acncer activity against aggressive breast cancer, with MNP-DHA being the most potent one[169]
Fe (III)-based framework	ART, Mn	A pH-responsive iron-based nMOFs that acts as an efficient amplifier for ferroptosis by depletion of intracellular GSH and by GSSH-mediated GPX4 inhibition, achieving a synergetic CDT-ferroptosis therapeutic efficacy in lung cancer[22]
MOF-5	pHCT74, DHA, CORM-401	A pH and GSH dual-responsive system with a passive enhanced permeability and retention effect, exhibiting specific targeting property against CRC and facilitating ROS-induced ferroptosis and apoptosis, which causes ICD and a sustained anti-tumor response[170]
$CaCO_3$-coated Fe(III)-TCPP	DHA	A pH-responsive iron-based nMOFs, which is well preserved during circulation, enables synergistic Fe(II)-DHA-mediated CDT, Ca^{2+}-DHA-mediated oncosis therapy, and TCPP-mediated photodynamic therapy, achieving enhanced anti-cancer efficacy[171]
Ca^{2+}-apoferritin	DHA	A self-targeting nano-platform that leverages calcicoptosis and ferroptosis dual therapy, extending the survival rate of breast cancer-bearing mice[172]
Zeolitic imidazolate framework-8	DHA	An acidic-responsible responsive framework enables controllable cancer-targeting release of Zn^{2+} and DHA, exerting anti-cancer activity in ovarian cancer through downregulation of ROMO1 and in taxane-resistant lung adenocarcinoma through down-regulation of Nrf2/HO-1 signaling and up-regulation of p38 MAPK signaling[173,174]
BSA, gold nanoclusters, MnO2	DHA	A self-reinforcing MnO2 nanozyme that induces oxidative stress and trigger Fenton reaction exclusively in the TME, which enables CDT and demonstrates favorable bio-imaging and anti-cancer activities[175]

DHA/AI/Ink@ALG that exhibits anti-cancer potency in hepatocellular carcinoma.[166] Upon intratumoral injection followed by in-situ irradiation with 1064 nm laser, AI rapidly decomposes into R• which not only exacerbates the mitochondrial damage synergistically with DHA-induced oxidative stress, leading to impaired ATP production, but also facilitates DHA-induced GLUT1 inhibition, leading to hindered glucose uptake.[166] Thus, this thermocontrolled starvation strategy affords efficient tumor-suppressive effects by achieving energy exhaustion in tumor cells.

pH Responsible

Cancer cells feature a hallmark of "reversed" pH gradient" with an intracellular pH that is higher than the extracellular pH, allowing the innovation of pH-dependent cytotoxicity against cancer cells, from virtually non-cytotoxic at physiological pH to highly toxic in acidic microenvironment.[178,179] By developing a pH-sensitive nanocarrier drug delivery

system, 4-Arm-PEG-DTX-DHA, that allows acid-triggered co-delivery of DHA and docetaxel preferentially to the acidic TME, Tao et al observe excellent inhibitory effects on the proliferation and aggressiveness of metastatic breast cancer cells.[158] Docetaxel (DTX) is an effective chemotherapy drug for breast cancer, but its therapeutic efficacy is unfavorable in metastatic breast cancer.[180] The anti-metastatic activity of 4-Arm-PEG-DTX-DHA is associated with decreased expression of phosphorylated protein kinase B (Akt), NF-κB and matrix metallopeptidase 2 (MMP-2).[158]

Zeolitic imidazolate framework-8 (ZIF-8) stands as an ideal drug carrier due to its pH responsiveness, hydrothermal stability, excellent monodispersity, and high drug loading capacity.[181] Yan et al develop an acidic-responsible responsive metal-organic framework loading DHA in the core of ZIF-8. ZIF-DHA collapses in the TME, enabling a controllable cancer-targeting release of Zn^{2+} and DHA, which exerts preferable pro-apoptosis and anti-cancer activity in ovarian cancer cells by downregulation of the reactive oxygen species modulator 1 (ROMO1).[173] ZIF-DHA also demonstrates enhanced anti-cancer effects of DHA in taxane-resistant human lung adenocarcinoma (A549-TAX) cells. This is achieved via down-regulation of Nrf2/HO-1 signaling as well as up-regulation of p38 MAPK signaling while with reduced side effects on normal cells.[174]

An acidic pH-responsive, Tf-decorated liposomal nanocarrier that encapsulates DHA, L-buthionine-sulfoximine (BSO), and CellROX (Tf-DBC NP) is implemented for efficient tumor eradication in HCC via amplification of oxidative stress, without inducing obvious oxidative injury to normal liver cells.[168] Tf-DBC NP achieves cancer-specific drug delivery via Tf-TfR binding and TfR-mediated endocytosis. The acidic environment within lysosomes activates Tf-DBC NP to release Fe(II), DHA, and BSO. Fe(II) can catalyze DHA to produce ROS, while BSO is a potent inhibitor of GSH synthesis. In addition, CellROX is a fluorescent probe for oxidative stress imaging, enabling in situ monition of the therapeutic efficacy. Tf-DBC NP thus offers a paradigm to achieve amplification of oxidative stress-mediated cancer theranostics.[168]

ROS/GSH Responsible

Cancer cells typically exhibit elevated levels of GSH and ROS, giving rise to the heterogeneity of TME in terms of oxidative and reductive stress.[182] Li et al design an redox-responsive DHA dimeric nanoprodrug bridged with disulfide bond (DHA2-SS) for the release of DHA under stimulation by TME triggers GSH and H_2O_2.[143] DHA2-SS can self-assemble into nanoparticles with high DHA content. Under oxidative stress, the disulfide bond of DHA2-SS is oxidized to hydrophilic sulfoxide or sulphone; while under reductive stress, the occurrence of sulfhydryl-disulfide bond exchange generates a thiol group. These reactions facilitate the hydrolysis of the adjacent ester bond, leading to DHA release. Compared with free DHA, DHA2-SS demonstrates more preferable anti-cancer activity in human hepatoma HepG2 cells xenograft mouse model by inducing apoptosis via mitochondrial apoptosis pathway, as well as glycolysis inhibition via down-regulation of PI3K/AKT/HIF-1α signaling.[143]

Nanoscale metal-organic framework (nMOF), which is created by inorganic metal nodes with organic bridging ligands, has been emerged as functional materials for diverse biomedical applications, due to its nontoxic nature, favorable biocompatibility and biodegradability, and controllable drug delivery.[22,171] Wang et al develop a cubic manganese oxide nanozyme (BSA-AuNC-MnO2@DHA) that integrates bovine serum albumin (BSA)-coated gold nanoclusters (AuNC) with MnO2 to encapsulate DHA, which confers favorable bio-imaging and anti-cancer activities.[175] MnO2 nanozymes are promising ROS-generating nanomedicines in chemodynamic therapy (CDT) which utilizes iron-initiated Fenton or Fenton-like reactions to eradicate tumor cells via converting less-active H_2O_2 into highly toxic ˙OH.[183] ·OH can irreversibly cause accumulation of lipid peroxide (LPO), leading to ferroptosis. Considering CDT is activated by the TME triggers, such as low pH and elevated ROS, CDT-mediated ROS production is exclusively achieved at tumor region and thus, exerting low toxicity and side effects on normal tissues.[184] As a self-reinforcing nanoreactor, MnO2 features both Fenton-like Mn^{2+} delivery and GSH depletion activities in the TME while with biodegradability.[185,186] BSA–AuNC–MnO2@DHA is shown to suppress tumor growth in LLC model by amplifying DHA-induced oxidative stress with exceptional biocompatibility and safety.[175]

Similarly, the pH-responsive iron-based nMOFs also effectively release Fe(II) to trigger tumor-specific Fenton reaction under acidic TME for tumor eradication. Wan et al develop a nanoplatform for the programmed delivery of DHA at tumor site using Fe-TCPP [(4,4,4,4-(porphine-5,10,15,20-tetrayl) tetrakis(benzoic acid)] nMOF.[171] Having

a $CaCO_3$ mineralized coating, the nanoplatform is preserved during circulation[187]. When arriving at the tumor site, the weakly acidic microenvironment and high levels of GSH trigger DHA release and TCPP activation, enabling the synergistic Fe(II)-DHA-mediated CDT, Ca^{2+}-DHA-mediated oncosis therapy, and TCPP-mediated photodynamic therapy, which achieves enhanced anti-cancer efficiency but with negligible toxicity.[171]

Yang et al develop an iron-based nMOFs for the co-release of DHA and iron ions (MIL-101@DHA) under the acid TME. The generated ˙OH thereupon causes ferroptosis and apoptosis in LLC cells.[22] In addition, DHA@MIL-101 can act as an efficient amplifier for ferroptosis by depletion of intracellular GSH (DHA@MIL-101 + GSH→Fe(II) + GSSH) and by GSSH-mediated GPX4 inhibition. The prominent anti-cancer activity of MIL-101@DHA with minimal systemic toxicity in LCC xenograft mouse model suggests this nanoreactor is a promising synergetic CDT-ferroptosis therapy for the treatment of lung cancer.[22]

By loading ART-based drugs into magnetic nanoparticle (MNP), Guo et al provide a framework to improve the therapeutic efficacy of CDT. Blank MNP is almost nontoxic, whereas MNP-ART, MNP-DHA, and MNP-AS demonstrate significant anti-cancer effects on drug-resistant breast cancer MCF-7/ADR cells, with MNP-DHA being the most potent one.[169] The pH-responsive MNP produces Fe(II) within the acidic TME, which thereby catalyzes DHA to produce ROS, leading to cell death. Furthermore, MNP-DHA exhibits inhibitory activity against another two aggressive breast cancer MDA-MB-231 cells and MDA-MB-453 cells, making MNP-DHA a promising therapeutic for the treatment of intractable breast cancers.[169]

pH and ROS/GSH Dual Responsible

By engineering a pH/ROS dual-responsive nanoenabled system PDBA@RSL-3, a preferential tumoral accumulation of DHA and RSL-3, a GPX4 inhibitor, is achieved.[165] DHA interacts with free ions to product carbon radicals and depletes intracellular glutathione, thereby synergizing with RSL-3 to potentiate ferroptotic therapy of pancreatic ductal adenocarcinoma (PDAC), one of the most lethal malignancies with resistance to conventional therapies, in both immune-deficient mouse models.[165,188,189] Importantly, PDBA@RSL-3 in combination with the programmed cell death protein 1 (PD-1) blockade immunotherapy affords attractive suppressive effect on PDAC aggressiveness in immune-competent mouse model, providing a novel hint for innovation of ferroptosis-based immunotherapy for PDAC treatment.[156,165,190]

Peng et al develop a pH/ROS dual-responsive lipid nanoparticle (LNP) for the co-delivery of DHA and chloroquine phosphate (CQ), an effective autophagy inhibitor. DHA and CQ are encapsulated within a lipid layer composed of soybean phospholipids (SPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), and 1,2-dioleoyl-sn-glycero -3-phosphocholine (DOPC).[163] SPC is susceptible to oxidation, leading to the formation of lipid peroxides, which increases the hydrophilicity of the lipid layer and compromises its structural integrity. DOPE imparts fusogenic properties to the liposomes, enabling them to escape from lysosomes in acidic environments.[163,191] Coating LNPs with cyclic arginylglycylaspartic acid (RGD) peptide, a specific ligand for the αvβ3 integrin, enhances the capability of the LNPs towards cancers that overexpress αvβ3 integrin, including CRC.[47] The resulting RGD-modified LNPs (RLNP/DC) exhibits enhanced anti-cancer effects of combination therapy with DHA and CQ in CRC. This is achieved by inducing oxidative stress via DHA-induced ROS generation and CQ-mediated autophagy suppression, inhibiting angiogenesis via downregulation of VEGF expression, and reducing metastasis via maintenance of the attachment between paxillin in cancer cells and integrin on extracellular matrix (ECM) via upregulation of paxillin expression.[163]

Su et al construct a pH and ROS dual-responsive autocatalytic release system (TPDM/PGA) by conjugating DHA and mitoxantrone to ROS-responsive polyethylenimine (TP) through a ROS-cleavable linker. This system is subsequently coated with pH-responsive polyglutamic acid (PGA). The dissociation of PGA within the TME facilitates its deep penetration and cellular internalization. Meanwhile, the ROS-responsive release of DHA and mitoxantrone creates a positive feedback to exacerbate oxidative stress. TPDM/PGA potentiates CRC immunotherapy and, when combined with PD-1 blockade immunotherapy, it significantly inhibits tumor growth and improves the survival of CRC-bearing mice.[167]

Yang et al develop a pH/GSH dual-responsive nanoenabled delivery system, pHCT74/MOF-5@DHA&CORM-401 (PMDC NPs), which enables efficient release of cargo, including DHA and CORM-401, in the TME with a passive enhanced permeability and retention effect. In addition, PMDC NPs exhibit specific targeting property against CRC due

to the pHCT74 peptide-mediated active targeting of overexpressed α-enolase on CRC cells. Mechanistically, DHA stimulates CORM-401 to release CO, facilitating ROS-induced ferroptosis and apoptosis, which causes ICD and a sustained anti-tumor response.[170] These findings indicate that the combined use of immunotherapy and gas therapy represents a promising therapeutic strategy for the treatment of CRC.

Therapeutic Activities of ARTs in Alzheimer's Disease

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive impairment, the histopathological features of which is the presence of extracellular β-amyloid (Aβ)-containing plaques and intracellular hyperphosphorylated tau-containing neurofibrillary tangles.[192,193] Aβ is generated from amyloid precursor protein (APP) via the amyloidogenic pathway, which is catalyzed by β-secretase (BACE1) and γ-secretase. The aggregation of Aβ can disrupt intercellular communication, induce neuroinflammation, and initiate tauopathy, all of which contribute to AD pathogenesis. ARTs are shown to beneficially mitigate AD pathology by regulating a wide spectrum of cellular processes, including Aβ deposition and the inflammatory response (Figure 5).

Reduction of Amyloidogenic Components' Expression

The administration of ART over a consecutive period of 30 days has been shown to decrease the brain expression of BACE1, resulting in the amelioration of neuritic plaque burden by approximately 61% in the hippocampus and 48% in the cortex of the APPswe/PS1dE9 (APP/PS1) transgenic mouse model of AD.[194] In a separate investigation, treatment with ART or AS for three months significantly diminished Aβ plaque load in the cortex and hippocampus of APP/PS1 mice, as evidenced by a decrease in the abundance of APP C-terminal fragments (APP-CTFs) and soluble Aβ in the hippocampus, suggesting a blocking of APP cleavage.[195,196] Notably, the preventive effects against amyloidosis were not observed at a high dosage of 100 mg/kg/day, highlighting the importance of considering dose-dependent effects in therapeutic applications.[195] Furthermore, oral administration of DHA for three months also led to a reduction in the presence of amyloid plaques in the cortex and hippocampus of male APP/PS1 mice, attributed to the downregulation of APP and BACE1 expression, without evident toxicity to the liver and kidneys.[197,198] The phenotypic traits associated with AD were similarly improved by AS, as indicated by a reduction in brain deposition of amyloid plaques in 5xFAD mice, another model of AD.[199] However, the brain expressions of amyloidogenic components, including APP, APP-

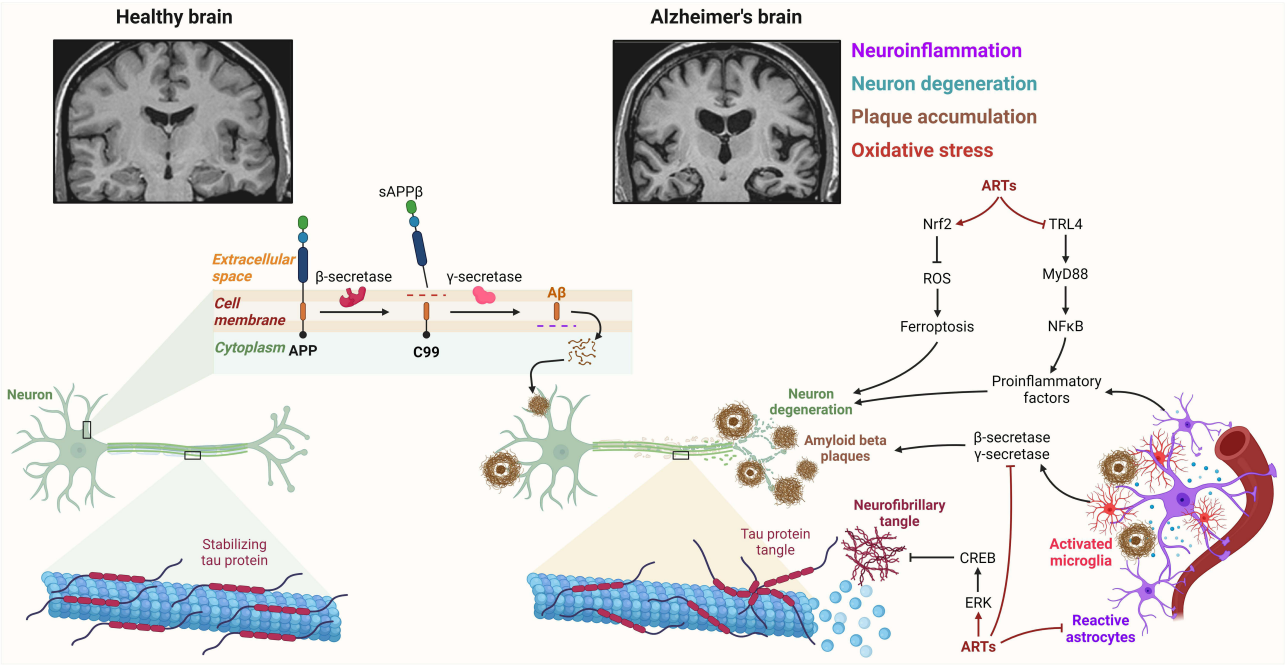

Figure 5 Therapeutic potential of ARTs in Alzheimer's disease by amelioration of amyloidopathy, tauopathy, and neuroinflammation.

CTFs, and BACE1, as well as Aβ-degrading enzymes such as neprilysin and insulin-degrading enzyme in 5xFAD mice, remained unchanged following AS treatment. This observation suggests the presence of alternative mechanisms involved in the elimination of amyloid plaques in AS-treated 5xFAD mice.[199] Collectively, these findings provide compelling evidence for the therapeutic potential of ARTs in mitigating AD's amyloid pathology.

Amelioration of Tau Pathology

It is well-established that regional interactions between Aβ and tau drive the propagation of tauopathy, which subsequently exacerbates amyloidopathy in AD.[200,201] Tau is a microtubule-associated protein that facilitates the organization and stabilization of microtubules, exhibiting high expression levels in axonal structures. In the context of AD, tau undergoes hyperphosphorylation, resulting in the formation of insoluble aggregates that can be transferred intercellularly. This process leads to the impairment of axonal transport, thereby compromising neuronal function and synaptic plasticity. Li et al (2019) documented the beneficial effects of ART following a four-week treatment regimen, which resulted in a reduction of amyloidopathy and tau pathology in the cortex of the 3xTg mouse model of AD. Furthermore, ART has been shown to ameliorate Aβ-induced cognitive impairments by downregulating the expression levels of Aβ, BACE1, and tau in N2a cells.[202] In 3xTg mice, treatment with ART or extracts from *Artemisia annua* significantly reduced the levels of Aβ deposition, neurofibrillary tangles, and tau hyperphosphorylation in both the cortex and hippocampus, without altering the total tau expression. This effect was observed in a dose-dependent manner and was mediated through the activation of the extracellular regulated protein kinases (ERK)/cAMP-response element binding protein (CREB) signaling pathways.[194,203]

Suppression of Inflammatory Response

Elevated levels of inflammatory markers in patients with AD and the involvement of AD risk genes in innate immunity suggest that neuroinflammation is a significant aspect of AD pathology.[204,205] Pro-inflammatory cytokines not only enhance amyloidopathy by upregulating BACE1 and γ-secretase but also exacerbate tau pathology by stimulating atypical cyclin-dependent kinase 5 (CDK5)-mediated tau hyperphosphorylation.[206,207] With important regulatory activities in neuroinflammation in central nervous system (CNS), glia cells including microglia and astrocyte exhibit spatial and temporal phenotypic variations in different settings.[205] Microglia cells are macrophages that represent less than 10% of brain cells. The activation of microglia at early stage of disease pathogenesis has neuroprotective effects by removal of harmful stimuli, while its persistent activation induced by the neurotoxic Aβ stimulates NF-κB signaling to incite the activation of NLRP3 inflammasome, thereby driving neurotoxicity. Inhibition of NLRP3 has been shown to ameliorate cognitive deficits in AD models.[208,209] Activated microglia also release several astrocyte-activating signals, including tumor necrosis factor alpha (TNF-α), interleukin-1, alpha (IL-1α), and complement component 1q (C1q).[210,211] Astrocytes, the most abundant glial cells in the brain, reside at the parenchymal part of the blood–brain barrier (BBB) that maintain the structural and functional integrity of BBB. Astrocytes possess the ability for Aβ clearance, which confers neuroprotective effects. However, when stimulated by neurotoxic Aβ or activated microglia, they exacerbate neuronal amyloidopathy by upregulating the expression of BACE1 and γ-secretase.[212,213] These findings indicate that modulation of glial activity may serve as a intervention strategy for AD.

Recent studies have demonstrated the anti-inflammatory effects of ARTs in AD mouse models. Specifically, *Artemisia annua* extract has been shown to reduce neuroinflammation in 12-month-old 3xTg mice by lowering the production of inflammatory cytokines while alleviating tau and amyloid pathologies.[203] In a separate study, ART treatment administered to 5-month-old APPswe/PS1dE9 mice over a 30-day period resulted in a reduction of NF-κB p65 nuclear translocation and an increase in I-κBα expression, leading to decreases of 37.16% and 34.46% in the production of IL-6 and TNF-α, respectively. Furthermore, ART treatment decreased NALP3 expression by 37% and reduced the production of caspase-1 p20 and IL-1β by 50% and 29.73%, respectively.[214] In 3xTg mice, intraperitoneal injection (i.p). of ART was found to attenuate the activation of glial cells and the expression of inflammatory factors.[194] In APPswe/PS1dE9 mice, administration of AS from 2 to 6 months of age effectively reduced the expression of TNF-α, IL-6, and IL-1β, while also improving alterations in mitochondrial dynamics.[196] Additionally, AS (32 mg/kg/day, i.p.) has been shown to suppress neuroinflammation in 5XFAD mice, evidenced by reduced activation of both microglia and astrocytes.[199] In

non-transgenic AD models, ART treatment was associated with an increase in IL-10 and a decrease in TNF-α in Aβ25-35-injected mice, while also significantly reducing glial activation in Aβ1-42-injected mice.[215,216] Notably, ART has demonstrated a protective effect on dopaminergic neurons by reducing microglial activation through the Toll-like receptor 4 (TLR4)/Myeloid differentiation factor 88 (MyD88)/NF-κB signaling pathway in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease mouse model.[217]

Mitigation of Oxidative Stress

Aβ can stimulate the production of reactive oxygen species (ROS) and ARTs can exhibit neuroprotective effects by mitigating oxidative stress in hippocampal neurons.[175,197,218,219] Ferroptosis is an iron-dependent form of non-apoptotic programmed cell death induced by overwhelming lipid peroxidation of biological membranes. It has important implications in a wide spectrum of diseases, including neurodegenerative disorders and type 2 diabetes mellitus (T2DM).[23,220,221] Epidemiological study suggests that individuals with type 2 diabetes are at approximate 60% greater risk for the development of dementia, and the diabetic cognitive deficits can be improved by ferroptosis inhibition.[222,223] ART effectively ameliorates neuropathological changes and cognitive impairments in T2DM mice by activation of Nrf2 to inhibit neuronal ferroptosis in the hippocampal CA1 region.[175]

ARTs in Improvement of Reproductive Health

Recently, ARTs have been identified as effective anti-polycystic ovary syndrome (PCOS) agents in both animal models and human patients. PCOS stands as the leading cause of female infertility, with an estimated heritability of 70% and a prevalence of ~15% in women of reproductive age. It is associated with a diverse lifetime risk of comorbidities, including hyperandrogenemia, hyperinsulinemia, and gynecological pathologies.[224] While accumulating evidence suggests that androgen and anti-Müllerian hormone (AMH) are contributing factors to PCOS through genetic or epigenetic mechanisms,[225–227] the etiology of PCOS remains largely unknown, making current interventions for PCOS are nonspecific and symptomatic. Recently, ARTs have been identified as effective anti-PCOS agents in both animal models and human patients. They work by inducing the degradation of cytochrome P450 11A1 (CYP11A1), which suppresses ovarian androgen synthesis.[18] ARTs can directly target lon peptidase 1 (LONP1), enhancing LONP1-CYP11A1 interaction and facilitating LONP1-driven CYP11A1 degradation. The phenotypes of this process can be replicated by LONP1 overexpression.[18] These findings present a novel therapeutic strategy for alleviating and treating PCOS.

Potential Reproductive Toxicity of ARTs: Evidence From Animal and Cohort Studies

Malaria in pregnancy is prevalent in malaria-endemic areas, being a clinically changeling infectious disease without effective drugs, partially due to drug resistance, to improve pregnancy outcomes.[228,229] Evidence from non-clinic studies suggests that single or consecutive treatment of ARTs in the first trimester of pregnancy is associated with embryolethality, due to the loss of circulating embryonic primitive erythroblasts, and teratogenic effects.[230,231] Cohort studies, however, suggest that first-trimester exposure to ARTs induces no adverse pregnancy outcomes in women with or without malaria infection.[228,230,232–234] ART-based combination therapies (ACTs), such as artesunate-amodiaquine, artesunate-mefloquine, artemether-lumefantrine, and DHA-piperaquine are proposed as favorable treatments for uncomplicated P falciparum malaria in the first trimester, compared to quinine-based therapy.[229,232–234] The adverse pregnancy outcomes, including miscarriage, stillbirth, low birth weight, small for gestational age and congenital anomalies and cardiovascular defects in newborns, are less seen in artemether-lumefantrine-exposed pregnancies, compared with that in quinine-exposed pregnancies, after anti-malarial treatment in the first, second, and third trimester.[228,232–238] It is accepted that the benefit of 3-d ATCs in the early pregnancy is likely to outweigh the unfavorable outcomes of partially treated malaria, which occurs with quinine treatment due to the known low tolerability and associated poor compliance to the 7-d regimen.[228,239]

The potential reproductive toxicity of ART should be considered seriously, as relatively low dosage is applied for only a few days for malaria therapy. Thus, drug accumulation over a prolonged period of treatment, which frequently arises

toxic side effects, is less possible. Indeed, the toxic effects are documented following prolonged treatment. In non-pregnant female rats, exposure to ART (7, 35, 70 mg/kg) for 7 consecutive days significantly increases the levels of hydrogen peroxide and malondialdehyde while decreasing the activity of catalase, glutathione peroxidase and superoxide dismutase in the erythrocytes and uterus, but not in the ovarian. The decreased follicle-stimulating hormone levels and increased levels of progesterone are also seen in ART-exposed females.[240] These findings indicate ART is a endocrine-disrupting chemical with oxidative toxicity. Similar oxidative toxicities are likewise observed in the epididymis, but not in the testes, of the male rats treated with ART (35 mg/kg) for 7 consecutive days.[241] While exhibiting no endocrine toxicity against the brain-pituitary-testicular axis, ART incurs severe degeneration in epididymis and impairment in sperm quality and quantity.[241]

Conclusion

Natural products serve as the foundation for discovering and developing novel therapeutic drugs, with a long history of global use for both preventive and therapeutic purposes.[242–252] ARTs represent a profoundly valuable class of natural compounds that have evolved from a traditional remedy into front-line anti-malarial drugs, now demonstrating significant potential for repurposing in oncology, neurology, and reproductive medicine[253]. The combination of ARTs with other pharmacological agents can produce synergistic therapeutic effects but may also lead to antagonistic toxicities. However, the successful translation of this potential into safe and effective clinical therapies is contingent upon overcoming critical challenges. A fundamental gap exists in our understanding of the therapeutic mechanisms of ART-based drugs at the molecular level, which hinders the rational design of optimized treatments and the prediction of off-target effects. Furthermore, while short-term use is well-tolerated, the safety profile of long-term, high-dose regimens-essential for treating chronic diseases like cancer-remains inadequately documented. The development of ART-based therapies must therefore be guided by rigorous preclinical and clinical safety evaluations, particularly as novel delivery systems like nanomaterials are explored.

Current Challenges and Future Perspectives

The development of ART-based drugs is constrained by several key limitations, including an ambiguous understanding of their molecular mechanisms, which hinders treatment optimization and prediction of off-target effects. Furthermore, their safety profile is incomplete, with a notable lack of documentation on the long-term side effects, especially at the high doses used in oncology. The application of nano-enabled delivery systems introduces additional concerns regarding the toxicity of the carriers themselves over extended treatments. Finally, while combination therapies offer promise, they also carry the risk of antagonistic interactions that could diminish efficacy or exacerbate toxicity.

Future research needs to focus on addressing current challenges to crack the full paradigm of ART-based therapy, primarily through detailed investigations to elucidate its ambiguous molecular mechanisms and provide a foundation for rational drug design. This should be coupled with laboratory-based mechanistic studies and advanced preclinical and long-term clinical trials to establish safety parameters for chronic use, particularly at high doses. Also, efforts should be devoted toward developing safer, more biocompatible nanocarriers for delivery and exploring novel formulations to improve bioavailability and targeting specificity. Finally, the integration of artificial intelligence for screening combination therapies and personalizing treatment regimens presents a powerful strategy to maximize synergistic efficacy while circumventing toxicity and antagonistic effects for individual patients.

Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI was used in scientific writing upon preparation of the paper.

Data Sharing Statement

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

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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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