Pharmacological activity, molecular mechanisms and therapeutic potential of erianin (Review)

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Received November 11, 2025; Accepted April 17, 2026

DOI: 10.3892/ijmm.2026.5854

Abstract. As a natural active ingredient extracted from *Dendrobium chrysotoxum*, erianin shows multi-target regulatory characteristics. The present review aimed to summarize the physiological effects, molecular mechanisms and therapeutic potential of erianin. Erianin has application bottlenecks such as poor water solubility and low bioavailability. The druggability of erianin could be effectively improved through structural modification, development of new drug delivery systems and combined drug use strategies. Although the *in vitro* synthesis process of erianin has been optimized for high yield and reproducibility, the *in vivo* toxicity and targeting need to be further optimized. The current review provides novel ideas for the systematic development of natural products, and guidance for promoting the clinical transformation of erianin.

Contents

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Key words: natural product, erianin, pharmacological activity, mechanism, application prospect

1. Introduction

The increasing global cancer burden, with an estimated 20 million new cases and 9.7 million deaths globally in 2022 with projections indicating a 77% increase in incidence by 2050 and the limitations of current treatments, which are exemplified by the fact that despite advancements in cancer detection, treatment and supportive care, survival outcomes remain suboptimal for many patients, together highlight an unmet need for novel therapeutic agents that are both effective and safe (1). There is an unmet need for novel therapeutic agents that are both effective and safe. Plant-derived natural products have attracted attention due to their extensive sources, low toxicity and side effects, high effectiveness and multi-target regulatory characteristics (2). *Dendrobium* has a long medicinal history and notable pharmacological activity (3).

Erianin is a bibenzyl complex ($C_{18}H_{22}O_5$; Fig. 1) extracted from *Dendrobium chrysotoxum* (4). This chemical structure endows erianin with a range of pharmacological activities, such as anticancer effects, anti-inflammatory effects, anti-angiogenesis (5). In recent years, studies have revealed that erianin exerts anticancer effects through multi-channel and multi-target mechanisms, including, promoting cancer cell apoptosis and inducing cell cycle arrest (5,6). However, despite its promising biological activity, the clinical development of erianin is hindered by its low water solubility and poor bioavailability, which limits its therapeutic efficacy *in vivo*. While previous literature has documented the pharmacological effects of erianin (6,7), to the best of our knowledge, there is a lack of comprehensive reviews that bridge the gap between its molecular mechanisms and the pharmaceutical strategies required to overcome its physicochemical limitations.

The present review aimed to systematically explain the anticancer basis of erianin through chemical characterization and pharmacological mechanisms, identify the specific limitations regarding its solubility and bioavailability, discuss future applications and delivery strategies to facilitate its development as a clinical drug and provide an example for the drug development of natural products.

2. Anticancer effects

Respiratory system

Lung cancer (LC). LC is a type of malignant cancer originating from trachea, bronchial mucosa or glands (8). Previous

research has revealed the multi-level mechanism of erianin against LC (9); its core role is derived from its unique biphenyl methyl structure, which enables it to specifically target and regulate the PI3K/Akt/mTOR signaling pathway (10). Notably, erianin induces ferroptosis by activating the Ca^{2+}/calmodulin signaling pathway (11). Therefore, erianin induces both apoptosis and ferroptosis (11).

At the level of metabolic regulation, erianin has shown precise intervention in cancer energy metabolism (12,13). Previous studies have confirmed that erianin has inhibits aerobic glycolysis in non-small cell LC (NSCLC) (2,14), which accounts for 85% of LC (14). Moreover, lung adenocarcinoma (LUAD) is estimated to account for 40% of all lung cancer cases (15). Erianin effectively inhibits the proliferation of cisplatin-resistant cells by regulating the Wnt3/β-catenin signaling pathway (16,17), which provides a novel possibility for overcoming common clinical chemotherapy resistance. In addition, erianin inhibits the proliferation, migration, invasion and angiogenesis of LUAD cells and induces apoptosis by regulating the multiple epidermal growth factor-like domains 9 (MEGF9)/MAPK/ERK signaling pathway (18).

Nasopharyngeal carcinoma. Nasopharyngeal carcinoma is a malignant cancer that originates from the nasopharyngeal mucosal epithelium. Erianin induces caspase cascade-dependent apoptosis, and blocks cell cycle progression by dually activating mitochondrial and death receptor pathways (19). At the same time, erianin inhibits ERK1/2 phosphorylation in a dose-dependent manner and promotes apoptosis by down-regulating MMP-9 expression. In conclusion, erianin inhibits nasopharyngeal carcinoma cell proliferation through the ERK1/2-MMP-9 signaling pathway (19). These findings reveal the multi-target anti-nasopharyngeal carcinoma mechanism of erianin and provide options for targeted therapy.

Digestive system

Liver cancer. Hepatocellular carcinoma, the main histological subtype of primary liver cancer, originates from the malignant transformation of liver parenchymal cells or mesenchymal tissue (20). Erianin affects the expression of cancer-associated genes by regulating pyruvate carboxylase (PC)-mediated Wnt/β-catenin signaling pathway, while promoting mitochondrial oxidative stress and inhibiting glycolysis and the proliferation of liver cancer cells (20).

At the molecular level, erianin induces ferroptosis by blocking the JAK2/STAT3/SLC7A11 signaling pathway (21) while regulating the PI3K/Akt and MAPK signaling pathways (22). Erianin can also activate the DNA damage repair pathway by inducing DNA damage, triggering G_2/M phase arrest and mitotic cell death, which is complementary to its metabolic regulation (23).

Erianin can simultaneously activate the mitochondrial apoptosis pathway (24) and oxidative stress response (25). Previous experiments in mice have demonstrated tumor growth inhibition without notable toxicity (21). Erianin can also regulate the immune microenvironment, which provides a theoretical basis for its combined application with other treatments, such as chemotherapy, biological immunotherapy, and traditional Chinese medicine (26).

Esophageal cancer (EC). EC is a highly malignant cancer type originating from the esophageal mucosal epithelium. Erianin can promote MMPs, block cell cycle progression and inhibit MAPK protein activation by dually regulating the JAK/STAT3 and MAPK signaling pathways, thus effectively blocking the proliferation and metastasis of EC cells (27).

In esophageal squamous cell carcinoma (ESCC), erianin exerts an anti-metastasis effect by promoting the ubiquitination and degradation of the outb deubiquitinase 1 (OTUB1) protein (28). Erianin also activates the cyclic guanosine monophosphate/cgmp-dependent protein kinase (cGMP/PKG) signaling pathway, induces apoptosis and inhibits ESCC cell migration (29).

Pancreatic cancer. Pancreatic cancer is a common and highly malignant digestive system cancer derived from pancreatic cells. For example, The American Cancer Society reports that PC is the 10th most common cancer in male and the 8th in female patients in terms of newly diagnosed cases (30). Previous research has shown that erianin significantly inhibits the proliferation and migration and induces the apoptosis of pancreatic cancer cells by dually regulating AKT/FOXO1 and apoptosis signal-regulating kinase 1 (ASK1)/JNK/p38 MAPK signaling pathways (31). Erianin directly interacts with MEK1/2 and blocks the activation of MAPK signaling, thus effectively inhibiting the proliferation of pancreatic cancer cells and the characteristics of cancer stem cells, including suppression of sphere-forming capacity and the downregulation of key stemness markers, such as CD133, CD 44, sex determining region y-box 2 (SOX 2), and octamer-binding transcription factor 4 (OCT 4) (32).

Oral cancer. Oral cancer is a malignant cancer that occurs in the oral cavity. Erianin induces the ferroptosis of oral cancer KB cells and inhibits their proliferation and metastasis by regulating the Nrf2/heme oxygenase-1 (HO-1)/glutathione peroxidase 4 (GPX4) signaling pathway (33). In oral squamous cell carcinoma, erianin exerts anticancer effects through a dual mechanism: Erianin blocks the cell cycle in the G_2/M phase, activates the apoptosis program and regulates autophagy (34) and induces autophagy-dependent apoptosis by inhibiting the palmitoyl-protein thioesterase 1/mTOR signaling pathway (35) and regulating the MAPK pathway (36).

Gastric cancer (GC). GC is a highly malignant cancer originating from the gastric mucosal epithelium. Erianin significantly inhibits the proliferation, invasion and migration of GC cells by dually regulating the PI3K/AKT and liver kinase b1/salt-inducible kinase 2 or 3/par-3 family cell polarity regulator (LKB1/SIK2/3/PARD3) signaling pathways (37). At the molecular level, erianin not only blocks the activation of the PI3K/AKT pathway, but also effectively reverses the epithelial-mesenchymal transition (EMT) of GC cells by inhibiting LKB1/SIK2/3/PARD3 signal transduction (38).

In addition, a previous study based on network pharmacology confirmed that erianin serves a key role in the treatment of gastric precancerous lesions by regulating the harvey rat sarcoma viral oncogene homolog (HRAS)/PI3K/AKT signaling pathway (39).

Colorectal cancer (CRC). CRC is a malignant cancer derived from the epithelial cells of the colon and rectum. Erianin significantly induces the apoptosis of CRC cells by dually regulating JNK and MAPK signaling pathways (40) and has a specific anticancer effect on BRAF V600 E or RAS mutant cells (41). In KRAS glycine-to-aspartic acid

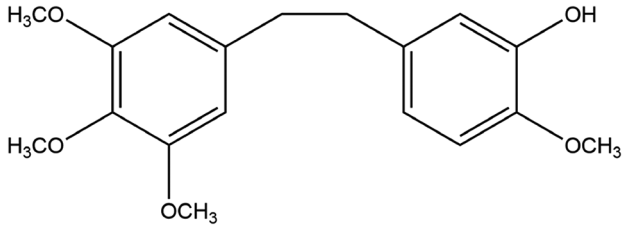

Figure 1. Chemical structure of erianin. The structure of erianin contains two polyphenol ethers and phenolic hydroxyl benzene rings, which are connected by two saturated carbon atoms. Erianin is a bibenzyl complex isolated from *Dendrobium chrysotoxum*.

substitution at codon 13 (G13D) mutant CRC, erianin effectively inhibits cancer cell migration, invasion and EMT by inducing autophagy-dependent ferroptosis (42,43). Erianin induces ferroptosis by promoting GPX4 ubiquitination degradation (44) and upregulating ferredoxin 1 expression (45).

Reproductive system

Breast cancer (BC). BC is a malignant cancer derived from breast epithelial cells (46). In triple-negative (TN)BC, erianin exerts anticancer effects through a dual mechanism: Erianin activates the mitochondrial apoptosis pathway and inhibits PI3K/Akt signal transduction (46,47) and regulates the cholesterol metabolism pathway by targeting sarcoma gene, which significantly inhibits cancer proliferation and migration (47,48). In estrogen receptor-positive BC, erianin effectively inhibits the proliferation and metastasis of T47D cells by regulating cell cycle progression, inducing apoptosis and balancing MMP/tissue inhibitor of metalloproteinase (TIMP) expression (49).

Erianin shows value in the treatment of bone metastasis of BC. As a novel nuclear factor of activated T cells, cytoplasmic 1 (NFATc1)-specific inhibitor, erianin can effectively block BC-induced pathological osteoclast genesis and decrease bone destruction in MDA-MB-231 breast cancer cell-induced bone loss mice (50).

Cervical cancer. Cervical cancer has the highest incidence of gynecological malignancy, with an incidence rate of 604,127 new cases reported in 2020 (51). Erianin shows a multi-level anticancer mechanism in the treatment of cervical cancer. In terms of immune regulation, erianin serves an important role through dual pathways: Erianin promotes the lysosomal degradation of PD-L1 and blocks the synthesis of hypoxia-inducible factor (HIF)-1α by inhibiting the mTOR/p70 ribosomal protein s6 kinase (S6K)/eukaryotic translation initiation factor 4e-binding protein 1 (4EBP1) pathway (52). Erianin also effectively restores the tumor killing ability of cytotoxic T lymphocytes by inhibiting the MAPK/ERK pathway (52). These immunomodulatory effects have been verified in *in vivo* experiments, showing anti-proliferative effects.

In terms of apoptosis regulation, erianin shows dose- and time-dependent anticancer properties (53). Erianin regulates the ERK1/2 signaling pathway, which causes HeLa cell cycle arrest in the G_2/M phase and activates the mitochondrial apoptotic pathway (53).

Endometrial carcinoma. Endometrial carcinoma is a malignant cancer originating from the endometrial epithelium. Erianin inhibits the proliferation and invasion of endometrial cancer cells by regulating the microRNA (miRNA or miR)-661/bcl-2-related ovarian killer signaling pathway (54).

Prostate cancer. Erianin has unique molecular mechanisms and therapeutic potential in the treatment of prostate cancer (55,56). Erianin increases the levels of C16 ceramide in androgen-sensitive prostate cancer cells, which is associated with the function of ceramide synthase 5 (CerS5) and triggers endoplasmic reticulum stress-associated apoptosis (56).

Nervous system

Glioblastoma (GBM). GBM is the most aggressive primary cancer of the central nervous system, GBM accounts for 45.6% of all primary brain malignancies. the incidence rate of GBM is 3.19 among 100,000 individuals from different age groups with a median age of 64 years (57). Erianin exhibits a dual cell death induction mechanism in the treatment of GBM (58). Erianin triggers GBM cell apoptosis by inhibiting the Bcl-2 protein and activating the bh3-interacting domain death agonist (Bid) protein (58). Erianin enhances the ferroptosis sensitivity of glioma stem cells and their temozolomide-resistant subsets by promoting the ubiquitination and degradation of the iron transporter SLC40A1 (59). This dual mechanism not only overcomes the drug resistance of the traditional chemotherapeutic drug temozolomide, but also improves the therapeutic effect by simultaneously targeting cancer cells and cancer stem cells. In addition, erianin inhibits EMT by targeting prolyl 4-hydroxylase subunit alpha 1, thereby restoring abnormal tumor blood vessels in GBM, reshaping the immunosuppressive tumor microenvironment and enhancing the efficacy of chimeric antigen receptor (CAR)-T immunotherapy and chemotherapy (60).

Neuroblastoma. Neuroblastoma is a malignant cancer originating from embryonic neural crest cells in the sympathetic nervous system (61). Erianin shows a multi-target anticancer mechanism in the treatment of neuroblastoma (3). Previous research has shown that erianin inhibits the malignant phenotype of SH-SY5Y cells through dual regulation: Erianin promotes the apoptosis of tumor cells by downregulating the expression levels of cancer-promoting *Homo sapiens* (hsa)-miR-155-5p and hsa-miR-223-3p (62).

Urinary system

Renal cell carcinoma (RCC). RCC is a highly heterogeneous malignant cancer derived from the renal tubular epithelial system. Erianin could promote N6-methyladenosine modification of arachidonate 12-lipoxygenase, 12s-type/P53 mRNA, regulate ferroptosis-associated signaling pathways and induce ferroptosis in renal cancer cells (63).

Bladder cancer. Bladder cancer is the second most prevalent malignant tumor of the urological system (5.85 cases per 100 000) (64). Erianin shows a multi-target anticancer mechanism in the treatment of bladder cancer (65). Specifically, erianin serves a key role through dual pathways: Erianin effectively induces ferroptosis in bladder cancer cells by inhibiting the NRF2 signaling pathway (65) and, by activating the JNK signaling pathway, triggers cell cycle G_2/M phase arrest and promotes apoptosis (66).

Skin system. Melanoma is a common and highly malignant cancer of the skin, it causes 75% of skin cancer-associated

mortality due to its high metastatic potential (64). Erianin exerts a significant effect through a dual mechanism: Erianin effectively promotes cancer cell apoptosis and inhibits cell migration by inhibiting the VEGF-α/PI3K/AKT signaling pathway (67) and inhibits the proliferation and survival of BRAF V600E or RAS mutant melanoma cells by simultaneously targeting MEK1/2 and c-raf proto oncogene serine/threonine protein kinase (CRAF) (41).

Blood. Leukemia is a common malignant clonal hematological disease that originates from bone marrow hematopoietic stem cells. Compared with 2020, by 2023, there were 2.4 additional instances per 100,000 people, and the fatality rate had increased to between 1.4 and 1.8 per 100,000 people (68). Erianin serves a significant role through dual pathways: Erianin effectively induces the death of acute myeloid leukemia cells by activating the PPARα signaling pathway and inhibiting PI3K/AKT signal transduction (69) and inhibits the proliferation and promotes the apoptosis of HL-60 leukemia cells by downregulating the expression of the anti-apoptotic protein Bcl-2, upregulating the expression of the pro-apoptotic protein Bax and arresting the cells in the G_2/M phase cell cycle (70).

Skeletal system

Osteosarcoma. Osteosarcoma is a common highly malignant bone cancer derived from osteoblasts, accounting for ~35% of all primary bone malignancies. The male-to-female ratio is ~1.5:1.0 (71). Previous *in vitro* and *in vivo* experiments have shown that erianin induces cell cycle G_2/M phase arrest, apoptosis and autophagy in human osteosarcoma cells by activating the reactive oxygen species (ROS)/JNK signaling pathway and serves an anticancer role (72). Notably, erianin significantly inhibited tumor growth in a xenograft mouse model without notable toxicity (72).

In conclusion, erianin has shown broad-spectrum anticancer activity in a variety of systems and cancer (Fig. 2; Table I). The underlying mechanisms include ferroptosis and anticancer effects by regulating core signaling pathways such as the PI3K/Akt/mTOR, JAK/STAT, MAPK and Wnt/β-catenin pathways (Fig. 3). The anticancer mechanism of erianin has been verified by a multi-disease model, which laid a foundation for clinical transformation. Compared with single highly selective targeted drugs, erianin has wider indications, overcomes cancer heterogeneity, has stronger clinical practicability, inhibits cancer in multiple systems, decreases drug resistance, is suitable for patients with advanced or multiple refractory cancer and has potential as a combination therapy (73).

The broad-spectrum anticancer biological activity of erianin is based on the precise regulation of key signaling networks (Fig. 3). Erianin induces specific cell death modalities such as ferroptosis via the JAK/STAT pathway and reverses chemotherapy resistance (21) and reprograms metabolism through the Wnt/β-catenin pathway (16). These converging mechanisms constitute the molecular basis for the universality and therapeutic potential of erianin against heterogeneous types of malignancy.

However, erianin may possess drug toxicity, and needs to balance efficacy and safety. A previous study found that erianin is stable, has low toxicity and shows consistent sensitivity and reliability in rat plasma under specific storage conditions (including long-term storage at low temperatures, short-term stability at room temperature and freeze-thaw cycle stability) (74), which provides a practical basis for clinical application.

3. Other effects

Complications of diabetes. Diabetes mellitus is a chronic metabolic disease characterized by persistent hyperglycemia (71). Erianin exerts multi-target regulation in the prevention and treatment of diabetic microvascular complications. Previous research has shown that erianin serves a protective role in diabetic retinopathy (DR) and diabetic nephropathy (DN) by co-targeting the NF-κB inflammatory pathway (75,76). In DR, erianin attenuates microglia-mediated retinal inflammation by inhibiting the ERK1/2-NF-κB signaling pathway (75), while blocking TNF-α-induced blood-retinal barrier damage (77).

In DN, erianin effectively protects renal tubular epithelial cells from high glucose injury by regulating the ROS/MAPK/NF-κB signaling pathway (76). These findings not only reveal the molecular basis of erianin in the prevention and treatment of diabetic microvascular complications through the dual mechanisms of anti-inflammation and anti-oxidative stress, but also provide a theoretical basis for the development of treatment strategies for diabetic complications based on natural products.

Diabetes is the leading cause of cardiovascular disease worldwide. Diabetic cardiomyopathy (DCM) is a complication with limited treatment options, as effective strategies remain elusive and glycemic control is still the primary approach (77,78). The hyperglycemic state in DCM disrupts cardiac energy metabolism and induces mitochondrial dysfunction, which represents a key pathological feature that is also implicated in other cardiac injuries such as myocardial ischemia-reperfusion injury (79). Erianin can effectively reduce myocardial injury, improve cardiac function and inhibit myocardial remodeling in a mouse model of type 2 diabetes by activating the AMPK/Nrf2/HO-1 signaling pathway (80). These findings not only reveal the cardioprotective effect of erianin through the dual mechanisms of antioxidant stress pathway (Nrf2/HO-1 mediated) and energy metabolism regulation (AMPK-dependent), but also provide a theoretical basis for the development of natural product-based DCM treatment strategies.

However, despite preclinical studies (5,8,11), erianin faces important challenges in practical applications. The optimal therapeutic dose and long-term safety of erianin are not clear, and there is a lack of large-scale clinical trial verification. Future research needs to focus on pharmacodynamic optimization and clinical transformation to realize the potential value of erianin in the treatment of diabetic complications.

Anti-angiogenesis. Erianin exhibits a multi-level inhibitory effect in the regulation of angiogenesis. In retinopathy, erianin inhibits inflammation-related angiogenesis by blocking the ERK1/2-NF-κB and HIF-1α/VEGF/VEGFR2 signaling pathways (81). By interfering with the collagen-integrin interaction, RhoA/ROCK1 signaling is inhibited to block collagen-mediated angiogenesis (82).

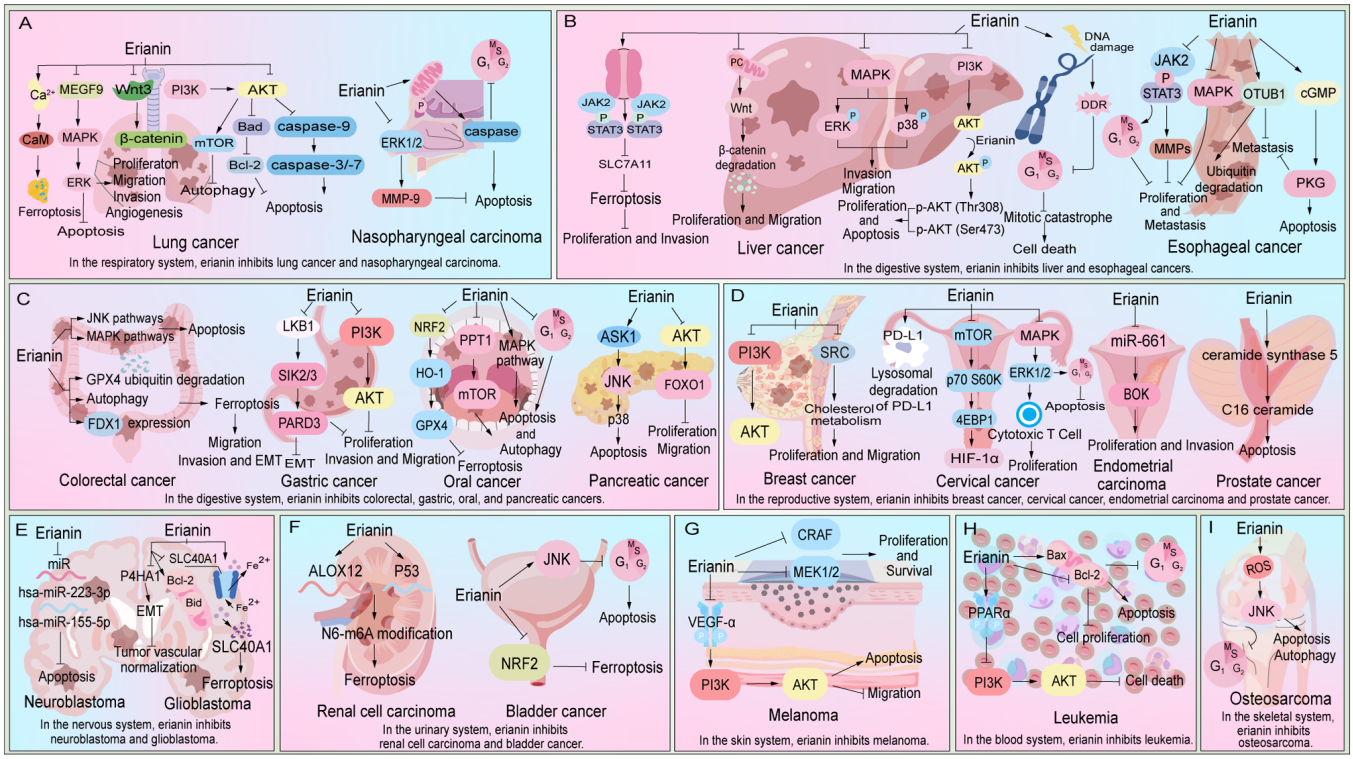

Figure 2. Mechanism of the broad-spectrum anticancer effect of erianin in human physiological systems. Erianin exerts therapeutic effects not merely through general cytotoxicity, but by modulating distinct signaling networks to trigger apoptosis, ferroptosis and cell cycle arrest across heterogeneous cancer types. (A) In the respiratory system, erianin suppresses lung cancer and nasopharyngeal carcinoma by inhibiting the PI3K/AKT/mTOR pathway and disrupting the ERK1/2/MMP-9 metastatic pathway, alongside inducing CaM-mediated ferroptosis. (B) In the digestive system (liver and esophageal cancers), erianin combats tumors by inducing ferroptosis via the JAK2/STAT3/SLC7A11 pathway and disrupting Wnt/β-catenin signaling, alongside regulating PI3K/Akt and MAPK pathways. (C) In the digestive system (colorectal, gastric, oral, and pancreatic cancers), erianin suppresses malignancies by triggering ferroptosis through GPX4 regulation and the NRF2/HO-1 axis, while inhibiting PI3K/AKT and LKB1/SIK2/3/PARD3 signaling, alongside modulating JNK/MAPK pathways. (D) In the reproductive system, efficacy against breast cancer, cervical cancer, endometrial carcinoma and prostate cancer is driven by immune modulation (PD-L1 degradation), regulation of cholesterol metabolism (SRC signaling) and activation of ceramide-dependent apoptosis. (E) In the nervous system, erianin overcomes glioblastoma and neuroblastoma aggressiveness by inducing a dual cell death mechanism involving miR-mediated apoptosis and SLC40A1-dependent ferroptosis. (F) In the urinary system, therapeutic action in renal cell carcinoma and bladder cancer relies on epigenetic modulation (m6A) and oxidative stress induction via the NRF2 and JNK pathways. (G) In the skin system, erianin combats melanoma by inhibiting the VEGF-α/PI3K/AKT pathway and dual-targeting MEK1/2 and CRAF kinases. (H) In the blood system, erianin fights leukemia by activating PPARα signaling while inhibiting PI3K/AKT, and by downregulating Bcl-2 alongside upregulating Bax to induce apoptosis. (I) In the skeletal system, erianin inhibits osteosarcoma by activating the ROS/JNK signaling pathway, leading to cell cycle arrest, apoptosis, and autophagy. CaM, calmodulin; GPX4, glutathione peroxidase 4; miR, microRNA; m6A, n6-methyladenosine; ROS, reactive oxygen species; MEGF, multiple epidermal growth factor-like domains; PC, pyruvate carboxylase; OTUB, OTU deubiquitinase; cGMP, cyclic guanosine monophosphate; PKG, cGMP-dependent protein kinase; S60K, S6 kinase; 4EBP1, eukaryotic translation initiation factor 4e-binding protein 1; HIF, hypoxia-inducible factor; BOK, bcl-2-related ovarian killer; FDX, ferredoxin; LKB, liver kinase B; SIK, salt-inducible kinase; PARD, partitioning defective; EMT, epithelial-mesenchymal transition; HO, heme oxygenase; PPT, palmitoyl-protein thioesterase; ASK, apoptosis-signal-regulating kinase; P4HA1, prolyl 4-hydroxylase subunit alpha 1; ALOX, arachidonate lipoxygenase; CRAF, C-Raf proto oncogene serine/threonine protein kinase.

In the regulation of cancer angiogenesis, erianin exhibits multi-target characteristics, including inhibiting endothelial cell metabolism via the JNK/stress-activated protein kinase-dependent pathway and disrupting the cytoskeleton (F-actin and β-tubulin) to affect endothelial cell migration (83). In addition, erianin inhibits the proliferation of human umbilical vein endothelial cells and formation of vascular endothelium and weakens the adhesion to fibronectin and cross-collagen migration, thus inhibiting cancer angiogenesis (84). Furthermore, erianin protects endothelial cells from oxidative damage via the Nrf2 pathway (85) and downregulates the JAK2/STAT3 signaling pathway and its downstream effectors (86). The key features of the anti-angiogenic effects of erianin include targeting the key signaling pathways of angiogenesis and regulating the basic biological processes of endothelial cells, as well as both anti-inflammatory and antioxidant effects. This makes erianin a potential candidate for the treatment of angiogenesis-related diseases, and provides an important theoretical basis for the development of novel anti-angiogenesis strategies. However, its selective regulation mechanism of angiogenesis in different tissue remains to be further elucidated.

Anti-inflammation

Chronic inflammation. Erianin has shown extensive therapeutic potential in chronic inflammation-related diseases, such as ulcerative colitis, rheumatoid arthritis, osteoarthritis, chronic atrophic gastritis and psoriasis (87-94,95,96). Previous studies have shown that erianin exhibits anti-inflammatory activity by directly inhibiting the assembly and activation of NLRP3 inflammasomes (87,95). In ulcerative colitis, erianin serves a role through a dual mechanism: On the one hand, erianin reduces the expression of the pro-inflammation factors IL-6 and IL-8 by inhibiting the TLR4/TRAF6/NF-κB signaling

Table I. Anticancer effects of erianin.

Cancer	Cell	Pathway	Mechanism	(Refs.)
Lung	H1975	PI3K/AKT/mTOR; Ca^{2+}/CaM	Upregulation of Akt, Bax, caspase-3/9, ROS, E-cadherin, CaM, HMOX, Ca^{2+} and MDA Downregulation of Bcl-2, GSH, GPX4, SLC7A11, N-cadherin, vimentin, Snail, Slug and MMP-9	(10-12)
Non-small cell lung	HCC827	Akt/GSK3β; PI3K/Akt/mTOR	Downregulation of HK2, p-Akt, p-GSK3β and caspase-3	(16)
Lung adenocarcinoma	A549/DDP	Wnt/β-catenin; MEGF9/ MAPK/ERK	Upregulation of p-GSK-3β, β-catenin, p-β-catenin, Wnt3, Wnt3a, cyclin D1 and Bcl-2; downregulation of Bax, caspase-3, caspase-9 and survivin	(17,18)
Nasopharyngeal carcinoma	NPC-039 NPC-BM	ERK1/2	Upregulation of BaK, Fas, TNF-R2, DR4/5, RIP, Bim S, caspase-3/8/9, PARP and Bim; downregulation of Bcl-2, p-ERK1/2 and Bcl-xL; decreased $\Delta\Psi m$	(19)
Liver	HepG2 SMMC-7721; Huh7	JAK2/STAT3/ SLC7A11; Wnt/β-catenin; DDR; PI3K/AKT; MAPK	Increased levels of ROS, MDA, Fe^{2+} and DDR; decreased levels of GSH, SLC7A11, GPX4, PC, p-ERK and p-p38	(21-26)
Esophageal	Eca-109	JAK/STAT3; MAPK	Downregulation of p-STAT-3, p-MAPK, p-JNK, p-p38, p-ERK1 and ERK	(27)
Esophageal squamous cell carcinoma	KYSE-150; KYSE-410; KYSE-450; KYSE-30; KYSE-180; TE-1; TE-10; SHEE	cGMP/PKG	Increased ubiquitin-mediated degradation of OTUB1 protein and cGMP/PKG signaling	(28,29)
Pancreatic	PANC-1; MIA PaCa-2; BxPC-3; SW1990; L3.7	AKT/FOXO1; ASK1/JNK/p38 MAPK	Upregulation of E-cadherin, P21, p-ASK1, p-JNK and p-p38; downregulation of N-cadherin, vimentin, β-catenin, p-Rb, cyclin B1, p-AKT and p-FOXO1	(30-32)
Oral	KB	Nrf2/HO-1/GPX4	Increased levels of ROS, MDA and Fe^{2+}; decreased levels of GSH, GPX4, Nrf2, HO-1 and FTH1	(33)
Oral squamous cell carcinoma	WSU-HN4; SCC-9; CAL-27	PPT1/mTOR; MAPK	Upregulation of caspase-3/8/9, PARP, Bax, Bak, DR5, RIP, LC3-II, p-p38 and p-JNK1/2; downregulation of Bcl-2, Bcl-xL, P62, p-AKT, p-ERK1/2	(34-36)
Gastric	HGC-27	PI3K/AKT; LKB1/SIK2/3/ PARD3	Upregulation of LKB1, PARD3, caspase-3, PARP and E-cadherin; downregulation of SIK2/3, N-cadherin, vimentin, Snail and β-catenin	(37-39)
Colorectal	HCT116/ LOHP	MAPK; JNK	Downregulation of CRAF, MEK1/2, p-MEK1/2, p-ERK1/2, Bcl-2, Bcl-xL, β-catenin, c-Myc, cyclin D1, CD47 and p-CRAF; upregulation of PARP, Bax and Bak	(40-45)
Breast	MDA-MB-231; MDA-MB-468; EFM-192A	PI3K/AKT; JNK/c-Jun	Upregulation of MUC1, CDK1 and PLAU; downregulation of CCND1, PPARA, PDGFRB, ROCK2, PI3K and p-AKT	(47-50)
Cervical	HeLa; HCT-116; A549; Hep3B; HUVEC	mTOR/p70S6K/ 4EBP1 MAPK; ERK1/2; HIF-1α/PD-L1	Downregulation of PD-L1, p-ERK1/2 and Bcl-2; upregulation of TFEB, TFE3, MITF, p-AKT, p-GSK3β, p-mTOR, p53 and caspase-3	(52,53)

Table I. Continued.

Cancer	Cell	Pathway	Mechanism	(Refs.)
Endometrial carcinoma	Ishikawa; HEC-251	Not applicable	Upregulation of caspase-3 and Bok; downregulation of Bcl-2	(54)
Prostate	LNCaP; PC3	AR	Upregulation of caspase-3, PARP, IRE1α, p-eIF2α, Bim, LC3-II and C16 ceramide; downregulation of Bcl-2 and p62↓	(55,56)
Glioblastoma	GSCm01R; U87R	Not applicable	Upregulation of VE-cadherin and VEGFR2; downregulation of CD133, SOX2, OCT4, Nanog, Nestin, REST, GPX4, SLC7A11, glutaminase, P4HA1, FSP1, α-SMA, N-cadherin and, P4HA1	(58-60)
Neuroblastoma	SH-SY5Y	Not applicable	mRNA upregulation of caspase-3/7/8 mRNA, FADD, Bid and DR5; downregulation of hsa-miR-155-5p, hsa-miR-223-3p and Bcl-2 mRNA	(62)
Renal cell carcinoma	$CD44^+/CD105^+$ HuRCSCs	/	Downregulation of FTH1, GPX4, SLC7A11, IRP2, FTO and p53; upregulation of PTGS2, METTL3/14, WTAP, ALOX12 and global m6A modification	(63)
Bladder	EJ; T24	NRF2; JNK	Upregulation of NRF2, HO-1, xCT, glutaminase, E-cadherin, CAM, Ca^{2+} and ROS; downregulation of FTH1, GPX4, N-cadherin, vimentin, Slug, Snail, MMP-9 and GSH	(65,66)
Melanoma	C918; MUM-2B uveal melanoma	MAPK; VEGF-α/PI3K/AKT	Downregulation of CRAF, MEK1/2, p-mTOR, p-PI3K, p-AKT, VEGFR2 and VEGF-α	(41,67)
Leukemia	HL-60	MAPK; PI3K/AKT	Upregulation of Bax; downregulation of Bcl-2	(69,70)
Osteosarcoma	143B; MG63.2; Saos2; CCHO	ROS/JNK	Downregulation of cyclin B/D/E1, Bcl-2, Bcl-xl, survivin and p62; upregulation of p21, p27, PARP, caspase-3/8/9, LC3B-II and p-JNK	(72)

ΔΨm, mitochondrial membrane potential; ALOX12, arachidonate 12-lipoxygenase; AR, androgen receptor; ASK1, apoptosis signal-regulating kinase 1; Bak, Bcl-2 homologous antagonist/killer; Bid, Bh3-interacting domain death agonist; Bim, Bcl-2-like protein 11; Bok, Bcl2-related ovarian killer; CaM, calmodulin; CCND1, cyclin D1; CDK1, cyclin-dependent kinase 1; cGMP-PKG, cyclic guanosine monophosphate-protein kinase G; DDR, DNA damage response; DR4/DR5, death receptor 4/5; E-cadherin, epithelial cadherin; eIF2, eukaryotic initiation factor 2; FADD, fas-associated protein with death domain; FSP1, fibroblast-specific protein 1; FTH1, ferritin heavy chain 1; FTO, fat mass and obesity-associated protein; GSC, glioblastoma stem cell; GSH, glutathione; GSK3, glycogen synthase kinase 3; GPX4, glutathione peroxidase 4; HIF-1, hypoxia-inducible factor 1; HK2, hexokinase 2; HMOX1, heme oxygenase 1; HO-1, heme oxygenase 1. HuRCSC, human renal cancer stem cell; IRE1, inositol-requiring enzyme 1; IRP2, iron-responsive element-binding protein 2; LKB1, liver kinase B1; MDA, malondialdehyde; MEK1/2, MAPK/ERK kinase 1/2; MITF, microphthalmia-associated transcription factor; m6A, n6-methyladenosine; MUC1, mucin 1; N-cadherin, neural cadherin; OTUB1, OTU deubiquitinase, ubiquitin aldehyde-binding 1; p70S6K, ribosomal protein S6 kinase β1; PARP, poly (ADP-ribose) polymerase; PARD3, par-3 family cell polarity regulator; P4HA1, prolyl 4-hydroxylase subunit α1; PC, pyruvate carboxylase; PD-L1, programmed death-ligand 1; PLAU, urokinase-type plasminogen activator; PPT1, palmitoyl-protein thioesterase 1; PTGS2, prostaglandin-endoperoxide synthase 2; REST, RE1-silencing transcription factor; RIP, receptor-interacting serine/threonine-protein kinase; ROCK2, rho-associated coiled-coil containing protein kinase 2; ROS, reactive oxygen species; SLC7A11, solute carrier family 7 member 11; TNF-R2, tumor necrosis factor receptor 2; VEGFR2, vascular endothelial growth factor receptor 2; WTAP, Wilms' tumor 1-associated protein; SMA, smooth muscle action.

pathway. On the other hand, erianin restores immune homeostasis by regulating the IL-2 levels (88). Similarly, erianin also has potential in the treatment of rheumatoid arthritis, where it inhibits the abnormal activation and polarization of T helper 17 cells by targeting the JAK/STAT3 signaling pathway (89). In addition, erianin serves a protective role in osteoarthritis by activating the GPX4/STING signaling pathway and inhibiting IL-1β-induced chondrocyte ferroptosis, oxidative stress and extracellular matrix degradation (90).

In chronic atrophic gastritis, erianin exhibits a regulatory role in maintaining autophagy homeostasis by balancing the activity of the MAPK/mTOR signaling pathway (91). The key core mechanisms of the anti-inflammatory effects of erianin include direct targeting of inflammasomes, regulation of key inflammation signaling pathways and maintenance of immune cell balance.

Psoriasis is a chronic recurrent inflammation skin disease characterized by excessive proliferation and abnormal

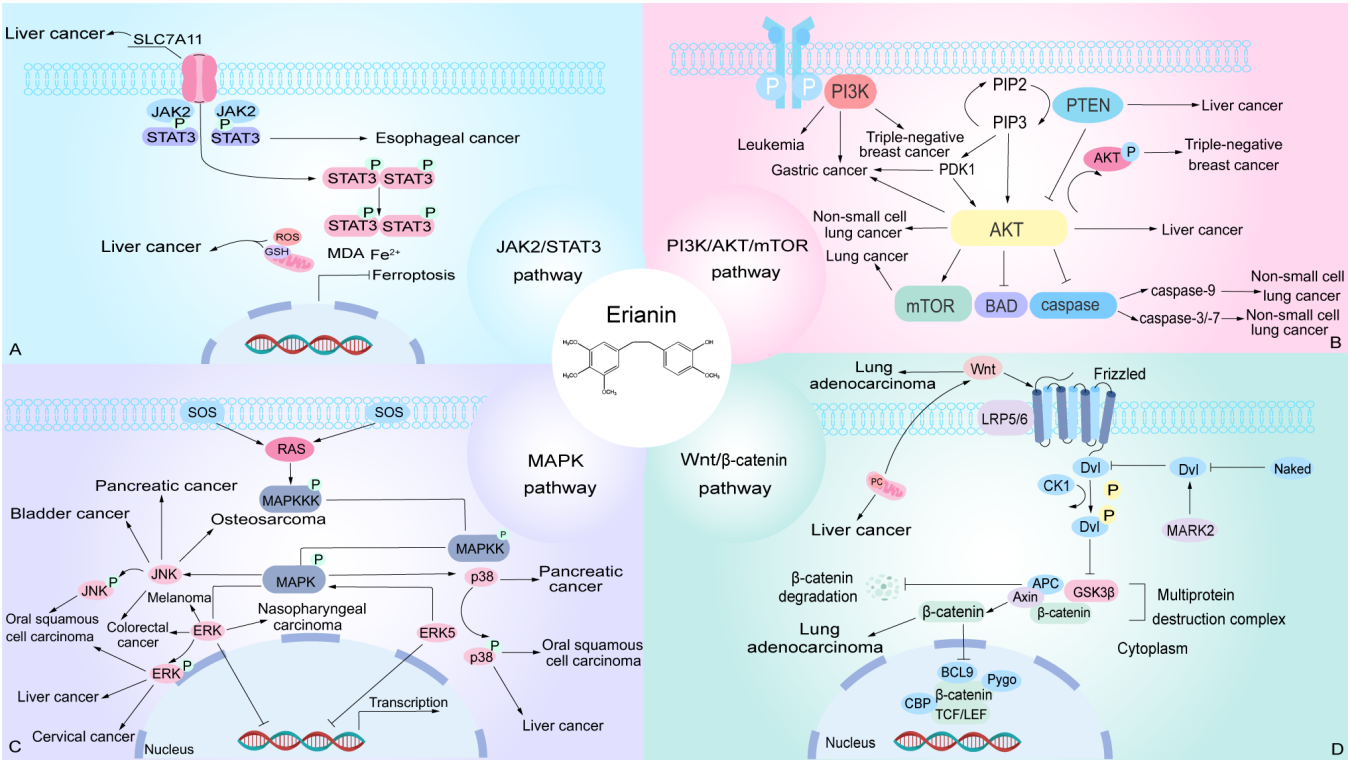

Figure 3. Anticancer mechanisms of erianin. Erianin shows versatility and act as a linchpin by regulating shared key signaling pathways. (A) Erianin can target liver and esophageal cancer through the JAK/STAT pathway to induce ferroptosis and block metastasis, downregulating SLC7A11 and disrupting the redox balance. (B) Erianin disrupts fundamental cell survival and proliferation cycles. This triggers caspase-dependent apoptosis and suppresses anti-apoptotic factors in lung, liver, gastric and triple-negative breast cancer as well as leukemia via the PI3K/Akt/mTOR pathway. (C) Erianin can exert multi-target control via the MAPK pathway, modulating JNK, ERK and p38 phosphorylation. This arrests the cell cycle and drives apoptosis in nasopharyngeal, liver, pancreatic, oral squamous cell, colorectal, cervical and bladder cancer, as well as osteosarcoma and melanoma. (D) Erianin can suppress metabolic reprogramming and reverse chemoresistance in liver cancer and lung adenocarcinoma by promoting the degradation of β-catenin and inhibiting its nuclear translocation, thereby regulating the Wnt/β-catenin pathway. ROS, reactive oxygen species; MDA, malondialdehyde; GSH, glutathione; PDK, pyruvate dehydrogenase kinase; PIP, phosphatidylinositol phosphate; BAD, bcl2-associated agonist of cell death; SOS, son of sevenless; MAPKKK, mitogen-activated protein kinase kinase kinase; LRP, low-density lipoprotein receptor-related protein; Dvl, dishevelled; CK, creatine kinase; MARK, microtubule affinity-regulating kinase; APC, adenomatous polyposis coli; GSK, glycogen synthase kinase; CBP, CREB-binding protein; TCF, T cell factor; LEF, lymphoid enhancer-binding factor.

differentiation of keratinocytes, resulting in impaired epidermal barrier function. Previous mechanistic studies have shown that erianin activates the JNK/c-Jun pathway in a ROS-dependent manner and inhibits AKT/mTOR signaling, thereby regulating the proliferation and differentiation of keratinocytes (92,96). These findings not only reveal the mechanism of erianin in the treatment of psoriasis, but also provide an experimental basis for the development of psoriasis treatment strategies based on ROS signal regulation.

Alopecia areata (AA) is a sudden-onset non-scarring hair disease (93). Erianin regulates the IFN-γ signaling pathway and inhibits cell populations closely related to the pathogenesis of AA (94). It is necessary to explore the causes and pathophysiological mechanisms of AA for the development of more effective treatment methods.

Acute inflammation. Myocarditis is a type of myocardial inflammation disease that leads to severe arrhythmia. It is the primary cause of dilated cardiomyopathy and may lead to heart failure (97). Erianin has shown notable anti-inflammatory activity and organ protection in acute inflammatory diseases, such as myocarditis and acute lung injury (98-100). In myocardial inflammation, erianin exerts therapeutic effects through a dual mechanism: Inhibiting the NF-κB and NLRP3 signaling pathways, decreasing M1 macrophage polarization and improving myocardial fibrosis and dysfunction to alleviate autoimmune myocarditis (98). By activating the Keap1/Nrf2 antioxidant pathway, reducing anthracycline-induced cardiotoxicity such as doxorubicin (DOX) and improving cardiac systolic function, erianin provides dual protection against chemotherapy-associated heart damage (99).

The lung is susceptible to acute inflammation and subsequent injury due to its extensive microvascular network and direct exposure to external stimuli. P-selectin is a potential therapeutic target for acute inflammation (100). Erianin mitigates lipopolysaccharide-induced acute lung injury in mice, reducing total cells, neutrophils and protein content in bronchoalveolar lavage fluid (BALF), as well as suppressing pro-inflammatory cytokines in both lung tissue and BALF (100).

In vivo, erianin inhibits NF-κB pathway activation in lung tissue, but does not attenuate inflammation responses in human pulmonary microvascular endothelial cells (HPMECs) *in vitro* (99). Mechanistically, erianin blocks neutrophil adhesion and transient adhesion-mediated movement along the surface of HPMECs by decreasing the binding affinity between P-selectin and p-selectin glycoprotein ligand-1 without altering P-selectin expression or membrane translocation (101).

This multi-target action characteristic makes erianin a potential candidate for the treatment of inflammation-associated diseases, and provides a theoretical basis for the development of new anti-inflammatory strategies.

Anti-virus. Human enterovirus 68 (EVD68) is an emerging viral pathogen that has received increasing attention due to its association with severe respiratory disease, such as asthma exacerbations, community-acquired pneumonia and typical acute respiratory illness (102-104). Erianin inhibits the production of EVD68 by inducing G_2/M blockade (105), thus suggesting the potential application of erianin in antiviral research.

Anti-oxidation. Oxygen free radicals and lipid peroxides are associated with the etiology of aging and diseases such as cancer, multiple sclerosis, Parkinson's disease, senile dementia, autoimmune disease and asbestosis (106). Erianin can effectively inhibit the abnormal activation of the ERK1/c-Jun signaling pathway following traumatic brain injury (TBI), and reduce oxidative stress and inflammation response in brain tissue (107). This reveals the antioxidant mechanism of erianin in TBI treatment.

Anti-drug resistance. Erianin exhibits a dual mechanism of action in overcoming cancer multidrug resistance (MDR). In an oxaliplatin-resistant model of colon cancer, erianin downregulates the expression of drug efflux protein P-glycoprotein (P-gp) by specifically inhibiting the JAK2/STAT3 signaling pathway, thereby effectively reversing the MDR phenotype of cancer cells (108). Erianin can also directly target the colchicine binding site of β-tubulin and impair the integrity of the cytoskeleton by inhibiting microtubule polymerization (109). This mechanism not only overcomes paclitaxel resistance (109), but also explains broad-spectrum anticancer activity of erianin.

Key mechanisms of erianin in overcoming cancer drug resistance include the regulation of drug transport systems and targeting of key components of the cytoskeleton, as well as the regulation of signaling pathways and direct cytotoxicity (108,109). This makes erianin a potential candidate drug to overcome cancer drug resistance, which provides a molecular mechanism basis and theoretical support for the development of novel MDR reversal strategies (109). Selective regulation mechanism of erianin on the resistance of different types of chemotherapeutic drug remains to be further elucidated.

Anti-bacteria. *Staphylococcus aureus* is a Gram-positive opportunistic pathogen. Sortase A (SrtA) is a key transpeptidase of Gram-positive bacteria. Erianin blocks the entry and binding of T-G peptide chain and lipid II of surface protein to the SrtA biological active center and effectively inhibits the anchoring function of transpeptidase (110). This finding reveals the mechanism of erianin against *S. aureus* infection and provides important theoretical basis and potential therapeutic targets for the development of novel anti-infection strategies based on SrtA inhibition.

Loss of neuronal protection. Erianin has shown neuroprotective effects in neurological diseases such as traumatic brain injury, cerebral ischemia-reperfusion injury and Parkinson's disease (105,111-113), and its mechanism of action primarily involves the regulation of key signaling pathways. In acute BI, erianin exerts a protective effect through a dual mechanism: In cerebral ischemia-reperfusion injury, erianin inhibits microglia-mediated neuroinflammation by regulating the PI3K/AKT and NF-κB pathways (111). In TBI, erianin attenuates neuronal injury by inhibiting the ERK1/c-Jun signaling pathway (105).

Erianin significantly alleviates neuroinflammation in a Parkinson's disease model by inhibiting the NF-κB/NLRP3 inflammasome pathway (112). Erianin promotes neuronal differentiation by regulating ERK1/c-Jun signaling (113). The aforementioned studies have revealed that the key mechanisms of neuroprotection of erianin include regulating the inflammatory response (NF-κB/NLRP3 pathway), maintaining neuronal survival (PI3K/AKT pathway) and promoting nerve regeneration (ERK1/c-Jun pathway). This makes erianin a potential candidate drug for the treatment of neurological disease and provides an important theoretical basis for the development of neuroprotection strategies based on signaling pathway regulation.

Anti-hepatic steatosis. Decreased vascular endothelial (VE)-cadherin expression in hepatic vascular endothelial cells is associated with hepatic steatosis in the early stage of non-alcoholic fatty liver disease (NAFLD); erianin could reduce hepatic steatosis by enhancing Nrf2-mediated VE-cadherin expression (114).

In conclusion, a number of studies have confirmed that erianin exhibits pharmacological activity beyond its antitumor activity (5,6). Erianin functions as a pleiotropic agent capable of restoring homeostasis across diverse pathological microenvironments (Fig. 4; Table II). Erianin is used in a treatments, ranging from reducing diabetic complications and inhibiting pathological angiogenesis, to alleviating acute and chronic inflammation, as well as for other biological activities, including neuroprotection, anti-hepatic steatosis, anti-microbial effects (antiviral and antibacterial), anti-oxidation and reversal of drug resistance. These bioactivities are driven by the ability of erianin to modulate key signaling pathways, primarily the inflammatory NF-κB/NLRP3 pathway, the oxidative stress-responsive Nrf2 pathway and cytoskeletal dynamics. By simultaneously targeting upstream receptors and downstream effectors, erianin serves as a multi-target candidate for complex disease management. However, the poor water solubility and low bioavailability of erianin limit its practical applications (6). In recent years, researchers have effectively improved the water solubility and bioavailability of erianin by chemical modification, new manufacturing technology and structural optimization (Fig. 5; Table III) (5).

4. Technological developments

Derivatives. The development of erianin derivatives has improved its anticancer efficacy and pharmacokinetic properties by structural modification. As a sulfamate derivative, Ecust 004 (Fig. S1) shows improved bioavailability and anti-breast cancer cell metastasis ability while retaining the activity of erianin and combretastatin A4 (CA4) (115).

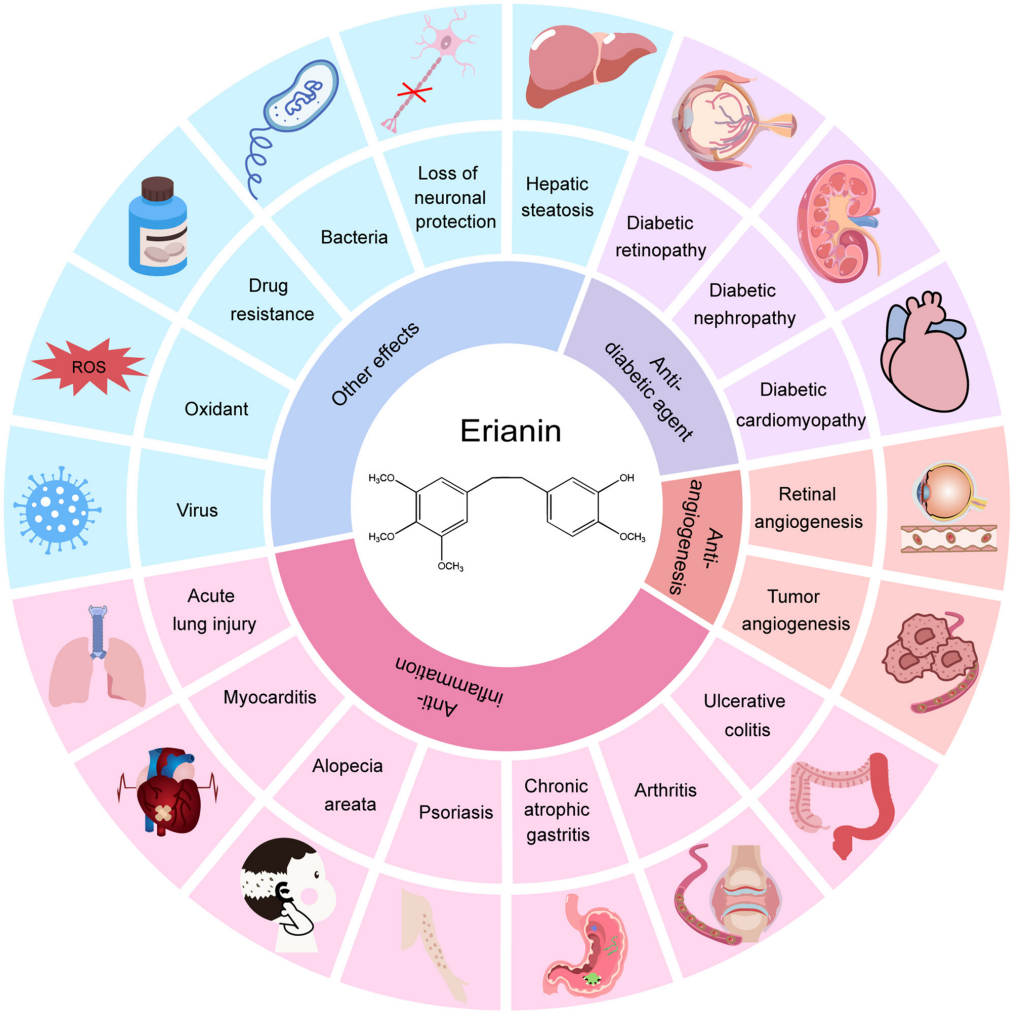

Figure 4. Multi-system therapeutic potential of erianin, Erianin mitigates diabetic complications, including diabetic retinopathy, nephropathy and cardiomyopathy by decreasing oxidative stress and inflammation. Erianin serves a role in inhibiting retinal and cancer angiogenesis. Erianin reverses chronic inflammation (such as ulcerative colitis, rheumatoid arthritis, osteoarthritis and chronic atrophic gastritis) and acute inflammation (such as myocarditis and pneumonia). Erianin exhibits anti-viral, antioxidant, anti-drug resistance, anti-bacterial, anti-psoriasis, anti-alopecia, neuroprotective and anti-hepatic steatosis effects.

Clinically, the importance of Ecust004 lies in its dual-targeting mechanism by serving both as a tubulin and steroid sulfatase inhibitor, which effectively induces G_2/M cell cycle arrest and reverses EMT, a key driver of metastasis, by upregulating E-cadherin and downregulating transcription factors such as SLUG and ZEB1 (115). However, the drug is in the preclinical experimental stage. While the sulfamate modification overcomes the obstacle of poor water solubility common in natural phenolic complexes, hurdles remain for clinical translation, including the need to address challenges associated with clinical scalability, targeting efficacy and the potential for off-target effects such as neurotoxicity and myelosuppression typically associated with tubulin inhibitors (115). Although preliminary *in vivo* studies have shown tumor suppression without significant weight loss in mice, extensive toxicology profiles are required to rule out off-target effects, particularly the neurotoxicity and myelosuppression typically associated with tubulin inhibitors (115). Furthermore, future research should clarify the precise molecular mechanism behind SLUG suppression and evaluate the scalability of chemical synthesis for potential pharmaceutical production (115).

Phosphorylated derivative EBTP (Fig. S2) inhibits the PI3K/Akt pathway by regulating the thymopoietin antisense RNA 1(TMPO-AS1)/miR-126-3p/PIK3R2 axis (116) and achieves VEGF/EGFR dual pathway inhibition in combination with afatinib (117). As a vascular blocker, EBTP has anti-proliferative effects and can inhibit the proliferation of breast, cervical, lung and liver cancer, as well as endothelial cells (117,118). EBTP is less toxic than CA4P, and inhibits the expression of indoleamine 2,3-dioxygenase, thereby inhibiting the migration and invasion of CRC cells (118).

From a translational perspective, EBTP represents a promising strategy for anti-angiogenic therapy. However, EBTP remains in the preclinical experimental stage. While molecular docking and RNA sequencing provide a theoretical foundation for its mechanism, obstacles regarding clinical scalability and targeting efficacy must be addressed (117). While regulating the long non-coding RNA/miRNA pathway offers high specificity, the systemic delivery of RNA-modulating drugs poses challenges, such as the risk of off-target effects, obstacles in clinical scalability, and challenges in targeting efficacy (117). Furthermore, although BALB/c nude mouse models suggest manageable toxicity, the potential off-target effects of systemic

Table II. Non-anticancer effects of erianin.

Disease	Pathway	Mechanism	(Refs.)
A, Diabetic complications			
Diabetic retinopathy	ERK1/2-NF-κB	Upregulation of occludin and claudin-1; downregulation of Iba1, NLRP3, ASC, caspase-1, p-IKK, p-IκB, p-p65, p-ERK1/2, GLUT1, p-c-Raf and p-MEK1/2	(75,77)
Diabetic nephropathy	JNK; MAPK; ROS/MAPK/NF-κB	Upregulation of caspase-3/9, Bax, ROS and MDA; downregulation of Bcl-2 and GSH	(76)
Diabetic cardiomyopathy	AMPK/Nrf2/HO-1	Downregulation of p-AMPKα, Nrf2, HO-1 and NQO1	(77,79)
B, Anti-angiogenesis			
Anti-retinal angiogenesis	ERK 1/2-NF-κB; HIF-1α/VEGF/VEGFR2; RhoA/ROCK1	Downregulation of integrin α2/β1, GTP-RhoA, ROCK1 and p-MYPT1	(81,82)
Anti-cancer angiogenesis	JNK/SAPK; JAK2/STAT3; Nrf2	Downregulation of p-STAT3, p-JAK2, MMP-2/9, HIF-1α, COX-2 and IL-6	(83-86)
C, Anti-inflammation			
Ulcerative colitis	JAK2/STAT3; NF-κB	Upregulation of TLR4, TRAF6, p-IKKα/β, p-IκBα, p-NF-κB p65, NF-κB p65, p-JAK2, p-STAT3 and p-Akt; downregulation of IκBα	(88)
Rheumatoid arthritis	JAK/STAT3	Downregulation of p-JAK2 and p-STAT3	(89)
Osteoarthritis	GPX4/STING	Upregulation of IL-1β, MMP-13, ADAMTS-5, iNOS, COX2, IL-6, TNF-α, p-TBK1 and p-IRF3; downregulation of p-GPX4, collagen II, aggrecan and STING	(90)
Chronic atrophic gastritis	MAPK/mTOR	Upregulation of P62/SQSTM1, LC3-II, Beclin1, p-p38 MAPK and p-mTOR	(91)
Psoriasis	JNK/c-Jun; Akt/mTOR	Upregulation of ROS, caspase-3, PARP, p-JNK, p-c-Jun and c-Jun; downregulation of p-AKT and p-mTOR	(92,96)
Alopecia areata	IFN-γ	Downregulation of MHC-I/II, GZMB+, PD-1+ and IFN-γ/IL-2	(94)
Myocarditis	NF-κB/NLRP3; Keap/Nrf2	Upregulation of Nrf2, HO-1, Bax, LC3B-II and SOD2; downregulation of Keap1, Bcl-2, P62 and P67	(97-99)
Acute lung injury	NF-κB	Upregulation of IκBα; downregulation of p-IκBα, p-p65, TNF-α, IL-6, IL-1β and PSGL-1/P-selectin binding	(100,101)
D, Anti-virus			
Human enterovirus 68	Not applicable	Downregulation of VP1, cyclin B1 and CDK1	(105)
E, Anti-oxidation			
Traumatic brain injury	ERK1/c-Jun	Upregulation of p-ERK1, p-c-Jun and c-Jun; downregulation of DCX	(107)

Table II. Continued.

F, Anti-drug resistance			
Disease	Pathway	Mechanism	(Refs.)
Oxaliplatin resistance	JAK2/STAT3	Upregulation of Bax; downregulation of Bcl-2, c-Myc, cyclin D1, HIF-1α, P-gp, p-JAK2 and p-STAT3	(108-109)
G, Anti-bacterial			
Staphylococcus aureus	/	Downregulation of SrtA	(110)
H, Loss of neuronal protection			
Traumatic brain injury	ERK1/c-Jun	Downregulation of MHC-I/II, GZMB+, PD-1+ and IFN-γ/IL-2	(105)
Cerebral ischemia-reperfusion injury	PI3K/AKT; NF-κB	Upregulation of Bax, caspase-3, CD86, CD32, COX-2, TNF-α, IL-6 and p-P65; downregulation of Bcl-2	(111)
Parkinson disease	NF-κB/NLRP3	Upregulation of GFAP, Iba-1, NLRP3, ASC, caspase-1, IL-1β, IL-18, NEK7 and p-NF-κB p65; downregulation of TH↓	(112)
I, Anti-hepatic steatosis			
Hepatic steatosis	Nrf2	Upregulation of VE-cadherin and N-Nrf2; downregulation of N-GATA4	(114)

ADAMTS-5, a disintegrin and metalloproteinase with thrombospondin motifs 5; AMPK, AMP-activated protein kinase; ASC, apoptosis-associated speck-like protein containing a CARD; CDK1, cyclin-dependent kinase 1; COX-2, cyclooxygenase-2; DCX, doublecortin; GATA4, GATA-binding protein 4; GFAP, glial fibrillary acidic protein; GLUT1, glucose transporter 1; GSH, glutathione; GZMB, granzyme B; HIF-1, hypoxia-inducible factor 1; HO-1, heme oxygenase 1; Iba-1, ionized calcium-binding adapter molecule 1; iNOS, inducible nitric oxide synthase; IKK, IκB kinase; LC3, microtubule-associated proteins 1A/1B light chain 3B; MDA, malondialdehyde; MEK, MAPK/ERK kinase; MHC-I, major histocompatibility complex class I; MYPT1, myosin phosphatase target subunit 1; NEK7, NIMA-related kinase 7; NLRP3, NOD-like receptor pyrin domain containing 3; NQO1, NAD(P)H quinone dehydrogenase 1; p-, phosphorylated; PARP, poly (ADP-ribose) polymerase; PD-1, programmed cell death protein 1; PI3K, phosphoinositide 3-kinase; P-gp, p-glycoprotein; TBK1, TANK-binding kinase 1; IRF3, interferon regulatory factor 3; GPX4, glutathione peroxidase 4; PSGL-1, p-selectin glycoprotein ligand-1; ROCK1, rho-associated coiled-coil containing protein kinase 1; ROS, reactive oxygen species; SAPK, stress-activated protein kinase; SOD2, superoxide dismutase 2; SQSTM1/p62, sequestosome 1; SrtA, sortase A; STING, stimulator of interferon genes; TH, tyrosine hydroxylase; TLR4, toll-like receptor 4; TNF, tumor necrosis factor; TRAF6, TNF receptor-associated factor 6; VEGFR2, vascular endothelial growth factor receptor 2.

PI3K/AKT pathway inhibition in human patients require evaluation in clinical trials (117,119).

Erianin-based histone deacetylase inhibitors (HDACis) and novel S derivative ZJU-6 have shown advantages through multi-target regulation (120). By incorporating a polar HDACi pharmacophore into the β-elemene scaffold, these hybrid agents address the limitations of antitumor activity and poor solubility found in the parent natural product (120). Combined regulation of epigenetics (HDAC inhibition) and signal transduction allows enhanced therapeutic outcomes. HDAC1/6 inhibitors 27f (Fig. S3) and 39f (Fig. S4) can effectively induce apoptosis, and 39f can also stimulate cell cycle arrest in G_1 phase (120). Consequently, these β-elemene-based HDACis provide an important paradigm for the development of natural product-based precise anti-lymphoma strategies, though structural optimization is required to ensure favorable pharmacokinetic profiles for clinical translation (120). ZJU-6 (Fig. S5) provides a direction for the study of pancreatic, breast and colon cancer by serving as a dual-action agent that inhibits tubulin polymerization and suppresses angiogenesis (121). However, ZJU-6 is currently in the preclinical stage. While it demonstrates superior anti-angiogenic properties and antioxidant capacity compared with erianin, it exhibits variable cytotoxicity across different cell lines (high potency in MDA-468 cells but decreased efficacy in MCF-7 cells) (121). Future research should clarify the target selectivity to

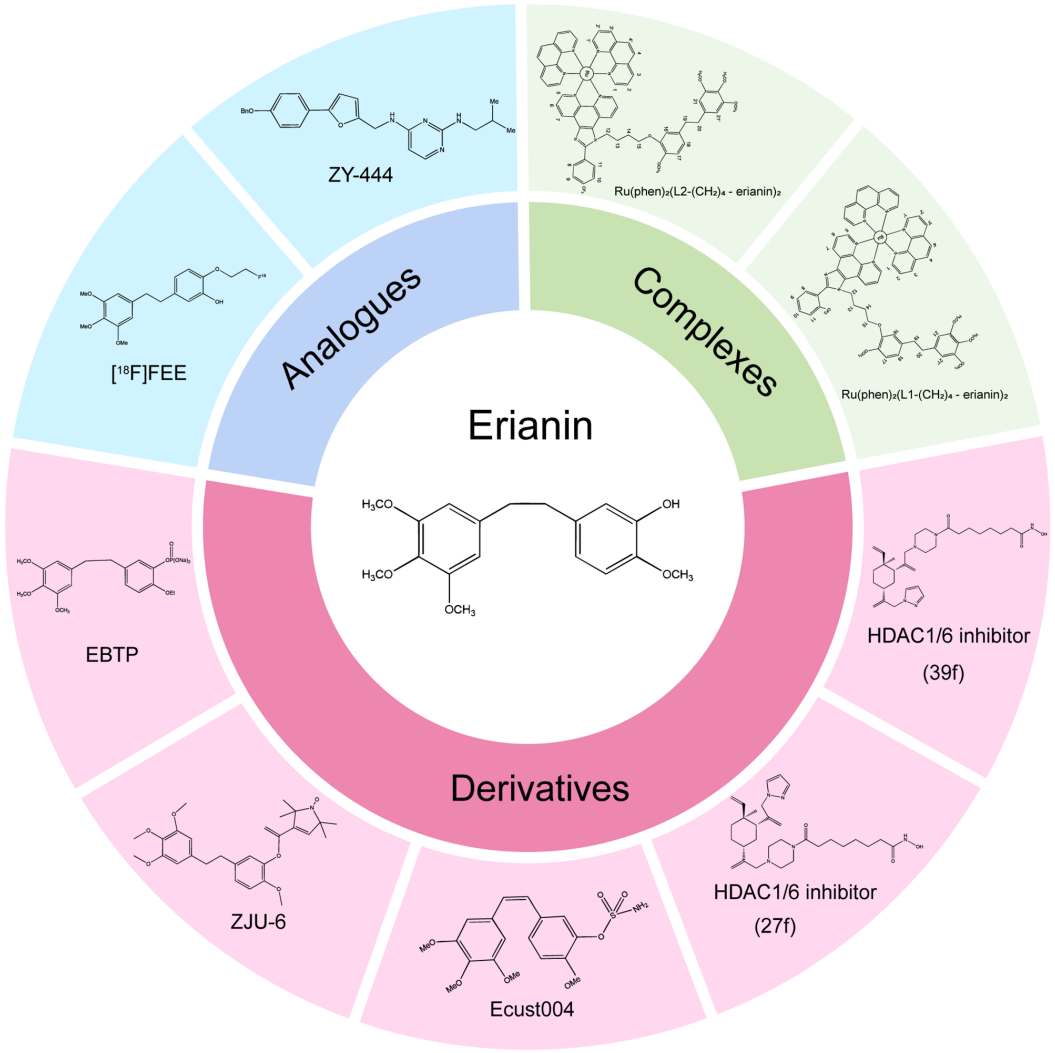

Figure 5. Strategic structural modifications of erianin. Derivatives are focused on enhancing bioavailability and multi-target effects to overcome drug resistance. Ecust 004 (sulfamate) serves as a dual tubulin/steroid sulfatase inhibitor to reverse epithelial-mesenchymal transition. Phosphorylated EBTP targets the PI3K/Akt pathway for anti-angiogenesis. HDAC1/6 inhibitors (27f and 39f) as well as ZJU-6 offer multi-target regulation of epigenetics and angiogenesis. Analogues are focused on metabolic targeting and theranostics. ZY-444 inhibits the metabolic enzyme pyruvate carboxylase in breast cancer, while [^{18}F]FEE facilitates PET imaging of hepatocellular carcinoma. Erianin-ruthenium (II) conjugates serve as G4 DNA stabilizers, suppressing c-myc oncogene expression through specific metal coordination. EBTP, 2-Ethoxy-5-(3,4,5-trimethoxyphenethyl)phenol phosphate disodium salt; HDAC, histone deacetylase.

overcome this sensitivity gap, evaluate *in vivo* mammalian toxicity and assess the combined drug potential of each derivative to determine clinical transformation feasibility.

Analogues. Erianin analogues have value in targeting the key enzyme PC of cancer metabolism. Previous studies have shown that PC, as a mitochondrial metabolic hub enzyme, is highly expressed in numerous types of cancer, such as hepatocellular carcinoma (122-124). Through the systematic structural modification of erianin, the inhibitory activity of ZY-444 (Fig. S6) on PC is increased, which provides a lead structure for the development of novel PC targeted inhibitors (125). However, the clinical transformation of ZY-444 appears to be limited. Despite its initial promise, to the best of our knowledge, no clinical trials have been reported thus far, likely due to its moderate potency compared with emerging natural product derivatives such as Ecust 004 (125). While targeting metabolic reprogramming remains a promising technology, the field faces obstacles regarding drug stability, oral bioavailability and the need for nanomolar affinity to ensure safety and efficacy (126-128).

In terms of diagnostic applications, the radiolabeled derivative [^{18}F]FEE (Fig. S7) allows PET imaging in a HepG2 liver cancer model by retaining the PC-targeting properties of erianin (129). The aforementioned study demonstrated that [^{18}F]FEE can be synthesized with high radiochemical purity via efficient nucleophilic substitution and exhibits favorable metabolic stability in serum. By retaining the specific properties of erianin (such as PC targeting or vascular disruption), [^{18}F]FEE demonstrates a time-dependent increase in the tumor-to-muscle ratio, allowing for distinct visualization of tumor borders in mice (129).

However, there are hurdles for clinical translation. Although the synthetic method is established and scalable, pharmacokinetics poses a challenge (129). Due to liver clearance, the uptake of tracers in tumors is not notably different from that in surrounding liver tissue (129). This high background signal is a significant obstacle for diagnosing primary

Table III. Structural modification of erianin.

Name	Mechanism	Cancer	(Refs.)
A, Derivatives			
Ecust 004	Upregulation of E-cadherin, α-catenin and vinculin; downregulation of SLUG	Breast	(115)
EBTP	Downregulation of PIK3R2, p-PI3K, p-AKT, VEGF-A, VEGFR1/VEGFR2 and lncRNA TMPO-AS1; upregulatio of miR-126-3p↑	Breast, cervical, colorectal, liver, lung	(116-118)
HDAC1/6 inhibitor 27f	Induces apoptosis	Lymphoma	(120)
HDAC1/6 inhibitor (39f)	Induces apoptosis; stimulates cell cycle arrest in G1 phase	Lymphoma	(120)
ZJU-6	Downregulation of Mcl-1 and Bcl-2; upregulation of PARP	Breast, colon, pancreatic	(121)
B, Analogues			
ZY-444	Inhibits PC	Liver	(125)
[^{18}F]FEE	Downregulation of EPK, JNK/c-Jun, AKT/mTOR, and MAPK signaling pathways, IDO expression, and VEGF/VEGFR2 signaling; upregulation of apoptosis, autophagy and G2/M phase cell cycle arrest.	Liver	(129)
C, Complexes			
$Ru(phen)_2$ $(L1\text{-}(CH_2)_4\text{-erianin})_2$	Increased stability of c-myc G-quadruplex	Breast, cervical, colon, small cell lung	(130)
$Ru(phen)_2$ $(L2\text{-}(CH_2)_4\text{-erianin})_2$	Increased stability of c-myc G-quadruplex	Breast, cervical, colon, small cell lung	(130)

AS1, antisense transcript 1; E-cadherin, epithelial cadherin; HDAC, histone deacetylase; Mcl-1, myeloid cell leukemia 1; lnc, long non-coding; miR-126-3p, microRNA-126-3p; PARP, poly (ADP-ribose) polymerase; PC, pyruvate carboxylase; PI3K, phosphoinositide 3-kinase; PIK3R2, phosphoinositide-3-kinase regulatory subunit 2; p-, phosphorylated; SLUG, Snail family transcriptional repressor 2; VEGFR1, vascular endothelial growth factor receptor 1.

hepatocellular carcinoma, potentially limiting the utility to extrahepatic metastases unless structural modifications alter its excretion pathway (129). Additionally, while analogues remain cytotoxic, the technology remains in the experimental preclinical stage, and issues regarding potential systemic toxicity and precise molecular binding specificity in humans remain unverified (125,129).

Despite these limitations, the aforementioned studies have established a dual-pathway clinical application framework of erianin analogues, including the development of therapeutic inhibitors based on PC targets and molecular imaging evaluation of PC expression levels. This strategy not only provides a potential candidate drug for the treatment of liver cancer, but may facilitate early diagnosis and efficacy monitoring of tumors, and has clinical transformation prospects. Future studies should verify the *in vivo* safety and target specificity of these analogues.

Complexes. The erianin-ruthenium (II) complex shows anticancer potential in the targeted regulation of G-quadruplex DNA (G4 DNA), which provides a novel concept for the study of breast, colon and cervical cancer and SCLC (130). Binding affinity and structural stability of complexes 1 and 2 formed by the coordination of erianin with ruthenium (II) (130) with G4 DNA in the promoter region of the c-myc gene are significantly enhanced. Complex 1 is $Ru(phen)_2(L1\text{-}(CH_2)_4\text{-erianin})_2$ (Fig. S8), while complex 2 is $Ru(phen)_2(L2\text{-}(CH_2)_4\text{-erianin})_2$ (Fig. S9). These complexes stabilize the advanced structure of c-myc G4 DNA through specific external binding and effectively inhibit the transcriptional expression of the c-myc proto-oncogene at the molecular level (130). The aforementioned study adopted a 'hybrid ligand' strategy, using erianin to enhance the targeting specificity of metal complexes. Complex 2 increases the melting temperature of

c-myc G4 DNA by 16.5˚C and exerts transcriptional inhibition by inserting into the narrow groove of DNA (the T19-A24 base pair region) (130). This provides novel insights for the development of epigenetically targeted drugs (130). However, technology remains in its early stages, and clinical translation faces multiple challenges, including lack of *in vivo* efficacy and metabolism validation and the need to improve selective recognition of c-myc G4 structures to avoid off-target toxicity. To the best of our knowledge, systemic toxicity, accumulation and metabolic stability have not been clearly defined and there are complex synthesis processes, high costs for large-scale production and stringent quality control requirements. Therefore, although complex 2 is a promising lead complex, future research should evaluate its pharmacokinetic properties in biological systems and overcome the technical bottlenecks associated with its transmembrane delivery and intracellular targeting. These findings not only provide a direction for the development of novel anticancer drugs based on epigenetic regulation, but also offer strategies to address the non-specific cytotoxicity associated with traditional chemotherapeutic agents.

Drug carrier modification

Nano-delivery system. The development of an erianin nano-delivery system has improved the clinical application bottleneck of this natural product. Solubility, targeting and therapeutic effect of erianin have been improved through preparation techniques (131). In cancer therapy, the DOX and erianin-loaded $CaCO_3$-based nanoparticles (DECaNPs) system shows multiple advantages, such as inducing calcium overload, neutralizing the acidic tumor microenvironment, activating oxidative stress damage, promoting immunogenic cell death, and enhancing immunotherapy (132). Similarly, the curcumin encapsulated nanoparticles (CEN) system combined with celastrol and erianin through self-assembly technology (133), shows benefits including enhancing cancer accumulation, improving drug solubility, and reduced systemic toxicity while maintaining potent anticancer activity. In the treatment of skin disease, the embedded dual-mesoporous silica nanoparticles (E/DMSNs) system enhances the inhibitory effect on keratinocytes through mitochondrial and endoplasmic reticulum stress pathways (134) and the light-responsive carrier achieves controlled release delivery of erianin (131).

Nano-delivery system solves the core problems of poor water solubility and low bioavailability of erianin (131). However, this technology faces three major challenges, including the balance between preparation stability and drug loading efficiency, optimization of large-scale production process and verification of long-term safety. Future research should aim to overcome these technical bottlenecks while maintaining targeted advantages to accelerate the clinical transformation of erianin nanoformulations.

Liposome delivery system. The erianin liposome delivery system provides an effective strategy to solve the poor aqueous solubility and off-target effects in its clinical application. Previous studies have shown that the solubility and targeting of erianin are improved by folic acid-chitosan modified dual drug-loaded liposomes (135) and transferrin-coupled liposomes (Tf-LP-ERN) (136). These systems enhance the accumulation of drugs in cancer cells through specific ligand-receptor interactions (such as folate receptor and transferrin receptor-mediated endocytosis), while using the sustained release characteristics of liposomes to prolong drug efficacy (136-138).

Although the liposome delivery system has good biocompatibility and high safety, it faces challenges, including complex preparation processes leading to batch-to-batch differences, poor physical stability affecting the storage period and high production costs restricting industrial production (136-138). Overcoming these technical bottlenecks is required to achieve the clinical application of erianin liposome preparations. In summary, carrier modification technology has a range of applications in erianin through nano-delivery and liposome delivery systems (Fig. 6).

5. Metabolism and practical application

The metabolic study of erianin provides a pharmacological basis for its clinical application. A total of 24 metabolites have been identified *in vitro* and *in vivo* by liquid chromatography/ultraviolet/mass spectrometry (138). The aforementioned study revealed that erianin undergoes extensive biotransformation involving specific pathways (hydroxylation, demethylation, and dehydrogenation in phase I; glucuronidation, glutathione, and N-acetylcysteine conjugation in phase II) and enzyme systems [cytochrome P450 (CYP) and uridine diphosphate-glucuronosyltransferases (UGTs)]. Metabolism is performed through different phase I and phase II reaction pathways. Previous metabolic studies have shown that erianin undergoes a complex biotransformation process (5,7). Hydroxylation, demethylation and dehydrogenation reactions mainly occur in phase I metabolism. These reactions are may be mediated by cytochrome P450 (CYP) enzymes that convert lipophilic prototype drugs into more polar intermediates (7,139). A key step involves the partial demethylation of trimethoxyphenyl to form a catechol group, which is unstable. In phase II metabolism, these reactive intermediates primarily combine with glutathione (GSH), glucuronic acid and N-acetylcysteine. The primary pathways differ depending on the species and substrate (7,139). In human liver cells and rat urine, glucuronidation (particularly metabolite M19) is the main detoxification pathway. GSH binding (metabolite M6) is the most abundant in rat bile, indicating significant bile excretion of reactive conjugates. These metabolic reactions change the physicochemical properties of erianin (7,139).

Extensive first-pass metabolism in hepatocytes is the primary reason for the low oral bioavailability and short half-life of erianin. Its glucuronide conjugates are readily excreted via the kidney due to their high polarity, while GSH conjugates are primarily cleared through bile (7,139). Catechol intermediates generated during metabolism are oxidized to reactive ortho-benzoquinones, which, as electrophilic complexes, bind intracellular nucleophiles (7,139). The detection of abundant GSH/n-acetylcysteine conjugates *in vivo* indicates that these reactive intermediates are captured by the antioxidant system (7,139). Although quinone metabolites typically carry the risk of hepatotoxicity, previous studies have found that glucuronidation competes with this bioactivation pathway, forming a detoxification mechanism, which may be an important reason for its clinical safety profile (7,139).

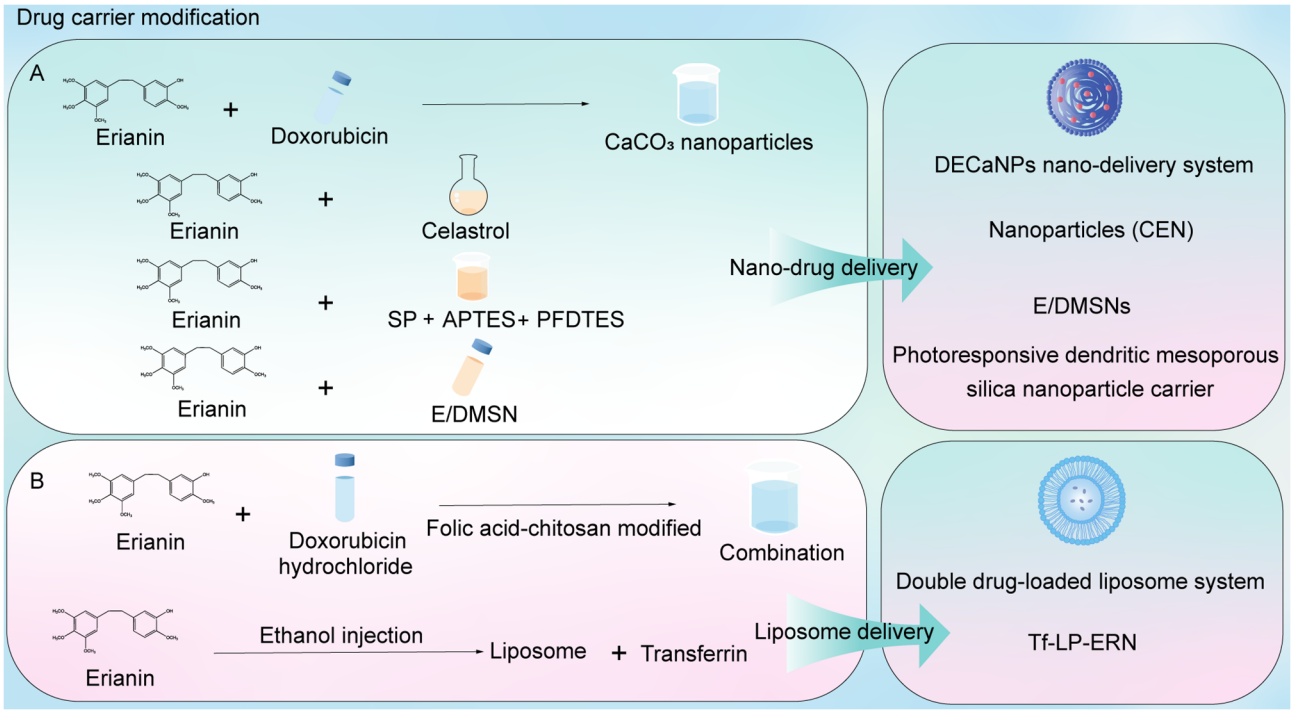

Figure 6. Nano-delivery systems and liposome-based carriers for erianin. (A) Nano-delivery systems (DECaNPs, CEN, E/DMSNs and photoresponsive dendritic mesoporous silica nanoparticle carriers) are designed to co-deliver erianin with chemotherapeutic agents. These systems enhance cancer accumulation, ameliorate the acidic microenvironment and promote systemic anticancer immunity. (B) Ligand-modified liposomal carriers (double drug-loaded liposomes system and Tf-LP-ERN) improve erianin solubility and targeting via receptor-mediated endocytosis. These liposomes exhibit sustained release and enhance drug accumulation at the disease site. DECaNP, doxorubicin and erianin-loaded $CaCO_3$-based nanoparticles; CEN, curcumin encapsulated nanoparticles; E/DMSN, embedded dual-mesoporous silica nanoparticles; Tf-LP-ERN, transferrin-conjugated liposome loaded with erianin; SP, substance P; APTES, 3-aminopropyltriethoxysilane; PFDTES, perfluorodecyltriethoxysilane.

In summary, the metabolism of erianin reflects a dynamic balance between the formation of reactive quinones (captured via GSH) and UGT-mediated glucuronide detoxification. Future studies should identify the relevant CYP/UGT subtypes to assess the risk of drug-drug interactions and validate the safety threshold for quinone formation and detoxification capacity in humans.

These metabolic characteristics are key for understanding the efficacy and safety of erianin. The diversity of metabolites suggests it may exert pharmacological effects through multiple pathways. GSH binding may be related to its antioxidant and cytoprotective effects (140-142). Glucuronidation affects its bioavailability and clearance rate (139). However, research on the activity of metabolites remains insufficient. It is necessary to clarify the pharmacological activity and toxicity characteristics of the primary metabolites in order to provide a more comprehensive scientific basis for the clinical rational use of erianin.

6. Biosynthesis and large-scale production

Systematic breakthroughs have been made in the research on the biosynthesis mechanism and large-scale production technology of erianin. A total of 11 key genes involved in bibenzyl synthesis in *D. officinale* has been identified (143) and the catalytic divergence mechanism of O-methyltransferase in p-methoxybenzyl synthesis has been demonstrated (144). A previous multi-omics integration study analyzed the complete biosynthetic pathway from gigantol (Fig. S10) to erianin (145), providing a key target for metabolic engineering. In terms of optimization of the extraction process, the petroleum ether extraction method shows industrial potential due to its high purity (146).

An economical and efficient route for the synthesis of erianin has been established: Using homovanillic acid and 3,4,5-trimethoxybenzaldehyde as starting materials, through the integrated process of hydroxyaldehyde condensation-microwave-assisted decarboxylation-mild reduction (147), the high cost and cumbersome steps in traditional synthesis has been solved.

The aforementioned studies have established the production system of erianin biosynthesis-chemical synthesis-extraction and purification, which provides a foundation for promoting its clinical application. Future research should focus on solving key issues such as the improvement of biosynthesis efficiency and the scale of extraction to accelerate the industrialization process.

Traditional production methods for erianin face a dual challenge: Scarcity of raw materials and the limitations of synthetic chemistry. Natural extraction from *D. chrysotoxum* is inefficient due to low yields (0.12%), creating a bottleneck for extensive applications. Furthermore, chemical synthesis is unsustainable due to its high economic cost and environmental footprint. These factors highlight a need to uncover the biosynthetic mechanisms for erianin production, thereby enabling the development of environmentally friendly biosynthetic manufacturing processes (145).

In summary, erianin has a wide range of pharmacological activities. The problems of poor water solubility and low

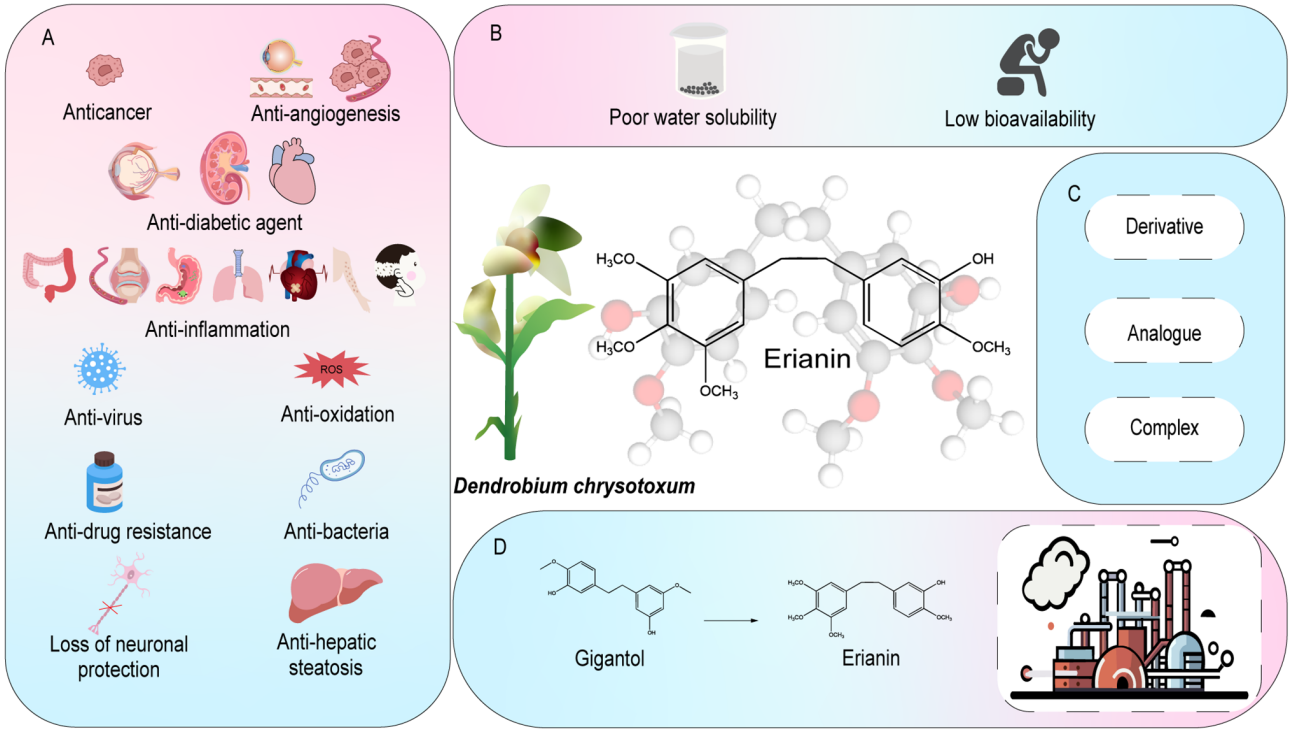

Figure 7. Research overview of erianin. (A) Erianin has a wide range of pharmacological activities. (B) Erianin exhibits poor water solubility and low bioavailability. (C) Derivatives, analogues and complexes have been designed by structural modification. (D) Synthesis of erianin from gigantol provides a theoretical basis for the biosynthesis and large-scale production industrialization of erianin.

bioavailability of erianin have been solved by chemical modification, preparation techniques and structural optimization and expanded to preclinical research, biosynthesis and large-scale production (Fig. 7).

7. Discussion

The natural product erianin has a range of pharmacological activities, most notably broad-spectrum anticancer effects by regulating multiple core signaling pathways and targets, such as the PI3K/AKT/mTOR, JAK/STAT, MAPK, and Wnt/β-catenin pathways. Previous studies focused on its pharmacological activity (5-7). In recent years, erianin has been found to have poor water solubility and low bioavailability, which limits its application as an anticancer drug (7). Therefore, methods such as structural and carrier modifications are being explored to promote the application of erianin. Structure-dependent activity and preclinical and clinical studies are essential to elucidate its pharmacokinetic characteristics and bioavailability (115,116,120).

The present review aimed to demonstrate pharmacological properties of erianin and establish a systematic paradigm for natural product drug research. This paradigm emphasizes a shift from the discovery of single active ingredients to multidimensional mechanistic analysis and the design of a full-chain pipeline leading to clinical translation. The transition of erianin from a traditional phytochemical to a potent lead complex exemplifies this paradigm.

Unlike conventional chemotherapeutic agents that typically rely on a single cytotoxic mode (DNA alkylation or tubulin inhibition), erianin exhibits pleiotropic pharmacological characteristics (5-7). By simultaneously orchestrating ferroptosis via the system xc-/GPX4 pathway (45,46), inducing mitochondrial apoptosis (20,26,47,54) and disrupting the tumor microenvironment (61) through anti-angiogenesis and immune modulation, erianin addresses the inherent heterogeneity of solid tumors. This multi-target strategy is advantageous in overcoming MDR, a prevalent problem in oncology. For example, the ability of erianin to downregulate P-gp while inducing ferroptosis suggests that it may be effective in refractory cancer cases where the apoptotic machinery is compromised (108).

To assess the potential of erianin it is necessary to compare its profile against established therapies. Conventional targeted therapies (tyrosine kinase inhibitors) (148,149) are typically limited by the rapid emergence of bypass signaling mutations. Erianin-induced broader inhibition of converging downstream hubs (PI3K/AKT/mTOR and MAPK) may create a higher barrier to resistance (23). However, compared with highly specific monoclonal antibodies, this polypharmacology introduces a risk of off-target toxicity, indicating that efficacy and safety must be balanced (150).

Compared with other natural products such as paclitaxel (151) or vincristine (152), erianin shares microtubule-destabilizing properties (109) but also exerts metabolic reprogramming (suppression of aerobic glycolysis and lipid metabolism) (7,139). However, erianin currently lags behind these established agents in pharmaceutical development. While the solubility issues of paclitaxel have been addressed through formulation strategies, erianin remains in the early stages of formulation optimization. The formation of reactive quinone metabolites identified in metabolic studies poses a risk of unpredictable hepatotoxicity similar to that observed with other phenol-containing drugs (such as acetaminophen),

necessitating rigorous benefit-risk assessments currently absent in the clinical literature. This druggability assessment requires confronting physicochemical defects and metabolic risks in addition to focusing on activity (7,139).

Despite promising preclinical data, the disparity between laboratory findings and clinical application remains an obstacle for erianin. The primary barriers are physicochemical (poor solubility) and pharmacokinetic (rapid metabolic clearance via glucuronidation) (7). The technological advancements reviewed in the present study, specifically the development of sulfamate (Ecust004) (115) and phosphate (EBTP) derivatives (118), demonstrate that structural modification can improve bioavailability without sacrificing potency. However, compared with the extraction of the parental complex, the reliance on chemical synthesis for these derivatives introduces complexity. Furthermore, the emergence of ruthenium-erianin complexes represents a paradigm shift from cytotoxicity to epigenetic modulation (stabilizing G4 DNA) (130). These strategies demonstrate how technological methods overcome the inherent limitations of natural products (7).

The lack of clinical data for erianin should be addressed not through broad-spectrum trials but via a precision medicine approach informed by the mechanistic insights highlighted in the present review. Based on preclinical evidence regarding ferroptosis and metabolic regulation, early-phase clinical trials should prioritize hepatocellular carcinoma and TNBC (22,24,49). Hepatocellular carcinoma is characterized by high iron load and metabolic dysregulation, making it susceptible to erianin-induced ferroptosis and GPX4 inhibition (22,24). Similarly, the aggressive, metastatic nature of TNBC aligns with the capacity of erianin to reverse EMT and inhibit metastasis (50). To maximize clinical success rates, patient selection should use biomarkers identified in mechanistic studies. High expression of SLC7A11 or GPX4 may serve as predictive biomarkers for sensitivity to erianin, while SLC40A1 levels may indicate susceptibility to iron-dependent cell death (22). Future drug development should focus on the balance between metabolic activation and detoxification. Clinical dosing regimens should be informed by quantitative pharmacology that accounts for the saturation of glucuronidation pathways. Furthermore, the development of sustained-release nanoformulations (such as the Tf-LP-ERN system) is key for maintaining therapeutic plasma concentrations and avoiding high fluctuations that may exacerbate toxicity (136). This roadmap constructs the clinical translation pathway, emphasizing a framework from mechanism to indication and from biomarkers to formulation optimization.

In conclusion, erianin represents a versatile chemical scaffold with the potential to address unmet needs in oncology and chronic inflammation. A shift from descriptive pharmacological studies to rigorous pharmacokinetic optimization and biomarker-guided translational trials is required.

8. Conclusion

Natural products have been widely used in the treatment of various diseases. Erianin is a low molecular weight natural product isolated from *D. chrysotoxum*, which has a wide range of pharmacological activities. The present study aimed to comprehensively review erianin, solving practical problems through chemical modification, preparation technology and structural optimization, and extends to preclinical research, biosynthesis and large-scale production.

Future studies on the design and synthesis of erianin derivatives may facilitate development of new drugs with improved pharmacological properties. In addition, the *in vitro* synthesis process of erianin is well-established (143-147), and its extensive pharmacological activity has also been verified (5-7). However, the structural modification and functional preparation of erianin are in the exploratory stage. A key direction of future research is to decrease the toxicity of erianin *in vivo* and maximize its efficacy at specific sites.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Hubei Provincial Natural Science Foundation and Xianning of China (grant no. 2025AFD393), the Science and Technology Research Project of Hubei Education Department (grant no. T2023024) and the Medical Scientific Research Project of Hubei University of Science and Technology (grant no. 2022YKY08).

Availability of data and materials

Not applicable.

Authors' contributions

CM wrote the manuscript and constructed figures. NZ, YY, HZ and MH wrote and editing the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ungvari Z, Fekete M, Varga P, Munkácsy G, Fekete JT, Lehoczki A, Buda A, Kiss C, Ungvari A and Győrffy B: Exercise and survival benefit in cancer patients: Evidence from a comprehensive meta-analysis. Geroscience 47: 5235-5255, 2025.
2. Khan AN, Jawarkar RD, Zaki MEA, Al Mutairi AA and Mali SN: Targeting PI3K/AKT/mTOR signalling pathway in non-small-cell lung carcinoma: Exploring promising bioactive natural compounds as anti-cancer agents. Chem Phys Impact 10: 100793, 2025.

3. Yan L, Zhang Z, Liu Y, Ren S, Zhu Z, Wei L, Feng J, Duan T, Sun X, Xie T and Sui X: Anticancer activity of erianin: Cancer-specific target prediction based on network pharmacology. Front Mol Biosci 9: 862932, 2022.
4. Zhang YY, Zhang QQ, Wei FH and Liu N: Progressive study of effects of erianin on anticancer activity. Onco Targets Ther 12: 5457-5465, 2019.
5. Wei X, Liu J, Xu Z, Wang D, Zhu Q, Chen Q and Xu W: Research progress on the pharmacological mechanism, in vivo metabolism and structural modification of Erianin. Biomed Pharmacother 173: 116295, 2024.
6. Li GM, Zhang HQ, Lai H, Liang G, Huang J, Zhao FL, Xie XF and Peng C: Erianin: A phytoestrogen with therapeutic potential. Front Pharmacol 14: 1197056, 2023.
7. Ma L, Li M, Zhang Y and Liu K: Recent advances of antitumor leading compound Erianin: Mechanisms of action and structural modification. Eur J Med Chem 261: 115844, 2023.
8. Yang LY and Wang ZL: Natural products, alone or in combination with FDA-approved drugs, to treat COVID-19 and lung cancer. Biomedicines 9: 689, 2021.
9. Zhao Y, Zhu S, Li Y, Niu X, Shang G, Zhou X, Yin J, Bao B, Cao Y, Cheng F, *et al*: Integrated component identification, network pharmacology, and experimental verification revealed mechanism of *Dendrobium* officinale Kimura et Migo against lung cancer. J Pharm Biomed Anal 243: 116077, 2024.
10. Zhang HQ, Xie XF, Li GM, Chen JR, Li MT, Xu X, Xiong QY, Chen GR, Yin YP, Peng F, *et al*: Erianin inhibits human lung cancer cell growth via PI3K/Akt/mTOR pathway in vitro and in vivo. Phytother Res 35: 4511-4525, 2021.
11. Chen P, Wu Q, Feng J, Yan L, Sun Y, Liu S, Xiang Y, Zhang M, Pan T, Chen X, *et al*: Erianin, a novel dibenzyl compound in *Dendrobium* extract, inhibits lung cancer cell growth and migration via calcium/calmodulin-dependent ferroptosis. Signal Transduct Target Ther 5: 51, 2020.
12. Yan LL, Liu YF, Huang YF, Sun XY, Jiang HY, Gu J, Xia J, Sun XN and Sui XB: Erianin inhibits the proliferation of lung cancer cells by suppressing mTOR activation and disrupting pyrimidine metabolism. Cancer Biol Med 22: 144-165, 2025.
13. Huang Q, Xu Y, Li H and Zhang T: Erianin inhibits endometrial cancer cell proliferation and migration by modulating glutamine metabolism through the ERK signaling pathway. Am J Transl Res 17: 8964-8972, 2025.
14. Han S, Chen S, Wang J, Huang S, Xiao Y and Deng G: Erianin promotes apoptosis and inhibits Akt-mediated aerobic glycolysis of cancer cells. J Cancer 15: 2380-2390, 2024.
15. Ping Z, Kui Z, Cuihua X, Sinan L and Xiang C: Role and clinical value of serum hsa_tsr011468 in lung adenocarcinoma. Mol Med Rep 30: 226, 2024.
16. Martin-Orozco E, Sanchez-Fernandez A, Ortiz-Parra I and Ayala-San Nicolas M: WNT signaling in tumors: The way to evade drugs and immunity. Front Immunol 10: 2854, 2019.
17. Tang L, Ruan Y, Wang B, Zhang M, Xue J and Wang T: Erianin inhibits the progression of DDP-resistant lung adenocarcinoma by regulating the Wnt/β-catenin pathway and activating the caspase-3 for apoptosis in vitro and in vivo. Hereditas 161: 48, 2024.
18. Ruan Y, Tang L, Zhou J, Li C and Wang T: Erianin suppresses lung adenocarcinoma by modulating miR-494-3p/MAPK/ERK pathway. Sci Rep 16: 10374, 2026.
19. Liu YT, Hsieh MJ, Lin JT, Chen G, Lin CC, Lo YS, Chuang YC, Hsi YT, Chen MK and Chou MC: Erianin induces cell apoptosis through ERK pathway in human nasopharyngeal carcinoma. Biomed Pharmacother 111: 262-269, 2019.
20. Hong J, Xie Z, Yang F, Jiang L, Jian T, Wang S, Guo Y and Huang X: Erianin suppresses proliferation and migration of cancer cells in a pyruvate carboxylase-dependent manner. Fitoterapia 157: 105136, 2022.
21. Sheng Y, Chen Y, Zeng Z, Wu W, Wang J, Ma Y, Lin Y, Zhang J, Huang Y, Li W, *et al*: Identification of pyruvate carboxylase as the cellular target of natural bibenzyls with potent anticancer activity against hepatocellular carcinoma via metabolic reprogramming. J Med Chem 65: 460-484, 2022.
22. Chen LY, Sun RR and Fang K: Erianin inhibits tumor growth by promoting ferroptosis and inhibiting invasion in hepatocellular carcinoma through the JAK2/STAT3/SLC7A11 pathway. Pathol Int 74: 119-128, 2024.
23. Yang L, Hu Y, Zhou G, Chen Q and Song Z: Erianin suppresses hepatocellular carcinoma cells through down-regulation of PI3K/AKT, p38 and ERK MAPK signaling pathways. Biosci Rep 40: BSR20193137, 2020.
24. Dong H, Wang M, Chang C, Sun M, Yang F, Li L, Feng M, Zhang L, Li Q, Zhu Y, *et al*: Erianin inhibits the oncogenic properties of hepatocellular carcinoma via inducing DNA damage and aberrant mitosis. Biochem Pharmacol 182: 114266, 2020.
25. Zhong M, He L, Shi YJ, Chen X and Ren JW: Induction of apoptosis in human hepatocellular carcinoma cells by erianin involves a mitochondria-mediated pathway. Curr Top Nutraceutical Res 19: 261-269, 2021.
26. Zhang X, Wang Y, Li X, Yang A, Li Z and Wang D: The anti-carcinogenesis properties of erianin in the modulation of oxidative stress-mediated apoptosis and immune response in liver cancer. Aging (Albany NY) 11: 10284-10300, 2019.
27. Hu A and Li K: Erianin impedes the proliferation and metastatic migration through suppression of STAT-3 phosphorylation in human esophageal cancer cells. Appl Biochem Biotechnol 196: 5859-5874, 2024.
28. Zhu Y, Kang N, Zhang L, Tao J, Xue W, Li H, Li Y, Zheng X, He W and Ma J: Targeting and degradation of OTUB1 by Erianin for antimetastasis in esophageal squamous cell carcinoma. Phytomedicine 135: 155969, 2024.
29. Deng X, Wu Q, Li D and Liu Y: Erianin exerts antineoplastic effects on esophageal squamous cell carcinoma cells by activating the cGMP-PKG signaling pathway. Nutr Cancer 75: 1473-1484, 2023.
30. Zhao J, Wang J, Gu Y, Huang X and Wang L: Diagnostic methods for pancreatic cancer and their clinical applications (review). Oncol Lett 30: 370, 2025.
31. Liu R, Qiu M, Deng X, Zhang M, Gao Z, Wang Y, Mei H, Zhai M, Zhang Q, Hao J, *et al*. Erianin inhibits the progression of pancreatic cancer by directly targeting AKT and ASK1. Cancer Cell Int 24: 348, 2024.
32. Zhu YR, Zhou S, Yang FQ, Zhang HS, Luo JX, Xie F, Liu DD, Lei YH and Deng LJ: Erianin inhibits the proliferation and stemness of pancreatic cancer cells by interacting with MEK1/2. Biochem Pharmacol 239: 117046, 2025.
33. Tian XY, Han R, Huang QY, Zhou MY, Luo B, Chen XR and Xu JC: Erianin inhibits oral cancer cell growth, migration, and invasion via the Nrf2/HO-1/GPX4 pathway. Asian Pac J Trop Biomed 12: 437-445, 2022.
34. Chen YT, Hsieh MJ, Chen PN, Weng CJ, Yang SF and Lin CW: Erianin induces apoptosis and autophagy in oral squamous cell carcinoma cells. Am J Chin Med 48: 183-200, 2020.
35. Luo Q, Li X, Gan G, Yang M, Chen X and Chen F: PPT1 reduction contributes to erianin-induced growth inhibition in oral squamous carcinoma cells. Front Cell Dev Biol 9: 764263, 2021.
36. Lin CW and Yang SF: Abstract 717: Erianin induces autophagy-dependent apoptosis in oral cancer cells. Cancer Res 79 (13 Suppl): S717, 2019.
37. Xu J, Qin N, Jiang W and Chen T: Erianin regulates PI3K/AKT signaling pathway and inhibits cell invasion and migration in gastric cancer in vitro. Curr Top Nutraceutical Res 20: 492-497, 2022.
38. Wei X, Liu Q, Liu L, Wang D, Liu J, Zhu Q, Xu Z, Chen Q and Xu W: Discovery of the natural Bibenzyl compound erianin in *Dendrobium* inhibiting the growth and EMT of gastric cancer through downregulating the LKB1-SIK2/3-PARD3 pathway. Int J Mol Sci 25: 7973, 2024.
39. Wang Y, Chu F, Lin J, Li Y, Johnson N, Zhang J, Gai C, Su Z, Cheng H, Wang L and Ding X: Erianin, the main active ingredient of *Dendrobium chrysotoxum* Lindl, inhibits precancerous lesions of gastric cancer (PLGC) through suppression of the HRAS-PI3K-AKT signaling pathway as revealed by network pharmacology and in vitro experimental verification. J Ethnopharmacol 279: 114399, 2021.
40. Tang J, Liu J, Zhang C, Zhou C and Chen J: Erianin induces apoptosis of colorectal cancer cells via activation of JNK signaling pathways. Int J Clin Exp Med 12: 11404-11411, 2019.
41. Wang P, Jia X, Lu B, Huang H, Liu J, Liu X, Wu Q, Hu Y, Li P, Wei H, *et al*: Erianin suppresses constitutive activation of MAPK signaling pathway by inhibition of CRAF and MEK1/2. Signal Transduct Target Ther 8: 96, 2023.
42. Miao Q, Deng WQ, Lyu WY, Sun ZT, Fan SR, Qi M, Qiu SH, Zhu YR, Lin JP, Chen MF and Deng LJ: Erianin inhibits the growth and metastasis through autophagy-dependent ferroptosis in $KRAS^{G13D}$ colorectal cancer. Free Radic Biol Med 204: 301-312, 2023.
43. Sun Y, Li G, Zhou Q, Shao D, Lv J and Zhou J: Dual targeting of cell growth and phagocytosis by erianin for human colorectal cancer. Drug Des Devel Ther 14: 3301-3313, 2020.

44. Zheng Y, Zheng Y, Chen H, Tan X, Zhang G, Kong M, Jiang R, Yu H, Shan K, Liu J, *et al*: Erianin triggers ferroptosis in colorectal cancer cells by facilitating the ubiquitination and degradation of GPX4. Phytomedicine 139: 156465, 2025.
45. Liu Y, Qian X, Li D and Qin Z: Erianin inhibits colorectal cancer cell malignant progression by inducing cuproptosis. J Biol Regul Homeost Agents 37: 6169-6178, 2023.
46. Xu Y, Fang R, Shao J and Cai Z: Erianin induces triple-negative breast cancer cells apoptosis by activating PI3K/Akt pathway. Biosci Rep 41: BSR20210093, 2021.
47. Li M, Zhao Y, Li H, Kang S, Deng X and Sheng M: Mechanism of Erianin anti-triple negative breast cancer based on transcriptomics methods and network pharmacology. Aging (Albany NY) 16: 2848-2865, 2024.
48. Li M, Kang S, Deng X, Li H, Zhao Y, Tang W and Sheng M: Erianin inhibits the progression of triple-negative breast cancer by suppressing SRC-mediated cholesterol metabolism. Cancer Cell Int 24: 166, 2024.
49. Sun J, Fu X, Wang Y, Liu Y, Zhang Y, Hao T and Hu X: Erianin inhibits the proliferation of T47D cells by inhibiting cell cycles, inducing apoptosis and suppressing migration. Am J Transl Res 8: 3077-3086, 2016.
50. Zheng J, He W, Chen Y, Li L, Liang Q, Dai W, Li R, Chen F, Chen Z, Tan Y and Li X: Erianin serves as an NFATc1 inhibitor to prevent breast cancer-induced osteoclastogenesis and bone destruction. J Adv Res 69: 399-411, 2025.
51. Sánchez-Meza LV, Bello-Rios C, Gómez-Gómez Y, Leyva-Vázquez MA, Araujo-Arcos LE, Duque JAV, Organista-Nava J and Illades-Aguiar B: Therapies and nanotherapies for cervical cancer (Review). Biomed Rep 23: 132, 2025.
52. Yang A, Li MY, Zhang ZH, Wang JY, Xing Y, Ri M, Jin CH, Xu GH, Piao LX, Jin HL, *et al*: Erianin regulates programmed cell death ligand 1 expression and enhances cytotoxic T lymphocyte activity. J Ethnopharmacol 273: 113598, 2021.
53. Li M, He Y, Peng C, Xie X and Hu G: Erianin inhibits human cervical cancer cell through regulation of tumor protein p53 via the extracellular signal-regulated kinase signaling pathway. Oncol Lett 16: 5006-5012, 2018.
54. Pang XC, Zhang X, Huang Y and Qian S: Erianin suppresses endometrial cancer progression by regulating the miR-661/BOK axis. Rev Bras Farmacogn 31: 805-813, 2021.
55. Yang Z, Liu R, Qiu M, Mei H, Hao J, Song T, Zhao K, Zou D, Wang H and Gao M: The roles of ERIANIN in tumor and innate immunity and its' perspectives in immunotherapy. Front Immunol 14: 1170754, 2023.
56. Trapika IGMGSC, Liu XT, Chung LH, Lai F, Xie C, Zhao Y, Cui S, Chen J, Tran C, Wang Q, *et al*: Ceramide regulates anti-tumor mechanisms of erianin in androgen-sensitive and castration-resistant prostate cancers. Front Oncol 11: 738078, 2021.
57. Al-Ghaithi AM, Al-Barkhati S, Al Abri AM, Al Husaini D, Al-Hajri A and Al-Saadi T: Palliative care in patients with glioblastoma: A systematic review. Med Int (Lond) 5: 46, 2025.
58. Serter Koçoğlu S, Seçme M and Elmas L: Erianin, a promising agent in the treatment of glioblastoma multiforme triggers apoptosis in U373 and A172 glioblastoma cells. Arch Biol Sci 74: 227-234, 2022.
59. Mansuer M, Zhou L, Wang C, Gao L and Jiang Y: Erianin induces ferroptosis in GSCs via REST/LRSAM1 mediated SLC40A1 ubiquitination to overcome TMZ resistance. Cell Death Dis 15: 522, 2024.
60. Zhou S, Qian S, Sun B, Shi P, Guo S, Yang C, Zhang J, Gong Y and Yang F: Vascular normalization by erianin unleashes CAR-T immunotherapy in glioblastoma. Angiogenesis 29: 18, 2026.
61. Podhorska N, Hrabeta J, Belhajova M and Eckschlager T: KDM5D expression is lost in cisplatin-resistant neuroblastoma cells. Oncol Rep 55: 79, 2026.
62. Kocoglu SS, Seçme M and Sunay FB: Erianin as a promising novel agent in the treatment of neuroblastoma: The anticancer effects and underlying molecular mechanisms. Anticancer Agents Med Chem 23: 1204-1210, 2023.
63. Shen H, Geng Z, Nie X and Liu T: Erianin induces ferroptosis of renal cancer stem cells via promoting ALOX12/P53 mRNA N6-methyladenosine modification. J Cancer 14: 367-378, 2023.
64. Zou Z, Yu Q, Yang Y, Wang F, Zhu P, Zhang X and Zhang J: Cytoglobin attenuates melanoma malignancy but protects melanoma cells from ferroptosis. Mol Med Rep 30: 219, 2024.
65. Xiang Y, Chen X, Wang W, Zhai L, Sun X, Feng J, Duan T, Zhang M, Pan T, Yan L, *et al*: Natural product erianin inhibits bladder cancer cell growth by inducing ferroptosis via NRF2 inactivation. Front Pharmacol 12: 775506, 2021.
66. Zhu Q, Sheng Y, Li W, Wang J, Ma Y, Du B and Tang Y: Erianin, a novel dibenzyl compound in *Dendrobium* extract, inhibits bladder cancer cell growth via the mitochondrial apoptosis and JNK pathways. Toxicol Appl Pharmacol 371: 41-54, 2019.
67. Sun H, Wang GL, Ren C, Zhang X, Zhao P and Guo B: Erianin inhibits cell migration and induces apoptosis by inhibiting VEGF-α/PI3K/AKT signaling pathway in malignant melanoma. Sci Rep 15: 15766, 2025.
68. Bose P and Bandyopadhyay S: A comprehensive assessment and classification of acute lymphocytic leukemia. Math Comput Appl 29: 45, 2024.
69. Deng Y, Zhong L, Zhao Y, Wan P, Zhang Y, Liao Y, Zhang H, Wang M and Liu B: A *Dendrobium chrysotoxum* extract erianin induce AML cells death by activating PPARα and downregulating PI3K/AKT signaling pathways. Toxicon 261: 108371, 2025.
70. Li YM, Wang HY and Liu GQ: Erianin induces apoptosis in human leukemia HL-60 cells. Acta Pharmacol Sin 22: 1018-1022, 2001.
71. Sugandh F, Chandio M, Raveena F, Kumar L, Karishma F, Khuwaja S, Memon UA, Bai K, Kashif M, Varrassi G, *et al*: Advances in the management of diabetes mellitus: A focus on personalized medicine. Cureus 15: e43697, 2023.
72. Wang H, Zhang T, Sun W, Wang Z, Zuo D, Zhou Z, Li S, Xu J, Yin F, Hua Y and Cai Z: Erianin induces G2/M-phase arrest, apoptosis, and autophagy via the ROS/JNK signaling pathway in human osteosarcoma cells in vitro and in vivo. Cell Death Dis 7: e2247, 2016.
73. Mei H, Qiu M, Liu R, Song T, Gao Z, Zhang Q, Wang Y, Hao J, Gao M, Yang Z and Wang H: Erianin induces GSDMD-dependent pyroptosis and synergistically enhances doxorubicin efficacy via the PI3K/AKT signaling pathway in diffuse large B-cell lymphoma. Chin Med J (Engl): Aug 20, 2025 (Epub ahead of print).
74. Yi X and Lan X: LC-MS/MS method for the determination of erianin in rat plasma: Application to a pharmacokinetic study. Biomed Chromatogr 34: e4826, 2020.
75. Zhang T, Ouyang H, Mei X, Lu B, Yu Z, Chen K, Wang Z and Ji L: Erianin alleviates diabetic retinopathy by reducing retinal inflammation initiated by microglial cells via inhibiting hyperglycemia-mediated ERK1/2-NF-κB signaling pathway. FASEB J 33: 11776-11790, 2019.
76. Chen MF, Liou SS, Kao ST and Liu IM: Erianin protects against high glucose-induced oxidative injury in renal tubular epithelial cells. Food Chem Toxicol 126: 97-105, 2019.
77. Li W, Xing Q, Liu Z, Liu R, Hu Y, Yan Q, Liu X and Zhang J: The signaling pathways of traditional Chinese medicine in treating diabetic retinopathy. Front Pharmacol 14: 1165649, 2023.
78. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW and Malanda B: IDF diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 138: 271-281, 2018.
79. Gao J, Li L, Zhai S, Dong Y, Zhang Z, Lin D and Ma J: Exercise training for myocardial ischemia reperfusion injury: Mechanism and clinical practice (review). Int J Mol Med 56: 191, 2025.
80. Chen JH, Dai XC, Quan ZJ and Liu XY: Erianin mitigates diabetic cardiomyopathy via adenosine monophosphate-activated protein kinase-nuclear factor erythroid 2-related factor 2-heme oxygenase-1 pathway activation. World J Diabetes 16: 103685, 2025.
81. Yu Z, Zhang T, Gong C, Sheng Y, Lu B, Zhou L, Ji L and Wang Z: Erianin inhibits high glucose-induced retinal angiogenesis via blocking ERK1/2-regulated HIF-1α-VEGF/VEGFR2 signaling pathway. Sci Rep 6: 34306, 2016.
82. Li X, Liu X, Xing Y, Zeng L, Liu X, Shen H and Ma J: Erianin controls collagen-mediated retinal angiogenesis via the RhoA/ROCK1 signaling pathway induced by the alpha2/beta1 integrin-collagen interaction. Invest Ophthalmol Vis Sci 63: 27, 2022.
83. Gong YQ, Fan Y, Wu DZ, Yang H, Hu ZB and Wang ZT: In vivo and in vitro evaluation of erianin, a novel anti-angiogenic agent. Eur J Cancer 40: 1554-1565, 2004.
84. Yang W, Chen D, Ji Q, Zheng J, Ma Y, Sun H, Zhang Q, Zhang J, He Y and Song T: Molecular mechanisms underlying the anticancer property of *Dendrobium* in various systems of the human body: A review. Biomed Pharmacother 165: 115223, 2023.
85. Wang Z, Wang L, Wang Y and Zhang J: Erianin protects human umbilical vein endothelial cells from oxidized low-density lipoprotein-induced apoptosis and oxidative stress through activation of nuclear factor E2-related factor 2 signaling. Chem Biol Drug Des 105: e70104, 2025.

86. Su C, Zhang P, Liu J and Cao Y: Erianin inhibits indoleamine 2,3-dioxygenase-induced tumor angiogenesis. Biomed Pharmacother 88: 521-528, 2017.
87. Zhang X, Hu L, Xu S, Ye C and Chen A: Erianin: A direct NLRP3 inhibitor with remarkable anti-inflammatory activity. Front Immunol 12: 739953, 2021.
88. Dou B, Hu W, Song M, Lee RJ, Zhang X and Wang D: Anti-inflammation of Erianin in dextran sulphate sodium-induced ulcerative colitis mice model via collaborative regulation of TLR4 and STAT3. Chem Biol Interact 324: 109089, 2020.
89. Tsai SW, Wang JH, Chang YK and Lin CC: Erianin alleviates collagen-induced arthritis in mice by inhibiting Th17 cell differentiation. Open Life Sci 18: 20220703, 2023.
90. Li C, Jian W, Lu S, Wang Y and Fang C: Erianin protects chondrocytes against IL-1β-induced oxidative stress and ferroptosis by activating GPX4/STING signaling in osteoarthritis. Inflamm Res 75: 19, 2026.
91. Jiang Q, Fan G and Wu K: Potential action mechanism of erianin in relieving MNNG-triggered chronic atrophic gastritis. Cell Biochem Biophys 83: 1035-1044, 2025.
92. Mo C, Shetti D and Wei K: Erianin inhibits proliferation and induces apoptosis of HaCaT cells via ROS-mediated JNK/c-Jun and AKT/mTOR signaling pathways. Molecules 24: 2727, 2019.
93. Zhang Y, Tang W, Tian W and Yu M: Research progress in regulation of hair growth by dermal adipose tissue. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 38: 626-632, 2024 (In Chinese).
94. Xuan X, Zhang G, Zhang J, Zhu Q, Zhang Y, Liu L, Peng D, Wang D and Liu Y: Mechanistic study of Erianin in alopecia areata. Am J Transl Res 17: 550-559, 2025.
95. Yan H and Wang G: Modulation of the KEAP1-NRF2 pathway by Erianin: A novel approach to reduce psoriasiform inflammation and inflammatory signaling. Open Life Sci 20: 20251139, 2025.
96. Ebrahimi A, Mohammadi P, Mirzaei SZ, Zavattaro E, Sadeghi M, Mehrabi M, Shabani S, Ranjbar S and Khodarahmi R: Exploring the interplay of PI3K/AKT/mTOR and JNK signaling pathways in psoriasis: Insights from systematic review and network pharmacology approach. Curr Pharm Biotechnol: Oct 2, 2025 (Epub ahead of print).
97. Ammirati E and Moslehi JJ: Diagnosis and treatment of acute myocarditis: A review. JAMA 329: 1098-1113, 2023.
98. Liu W, Mao Y, Li H, Hu J, Gan T, Wang Y, Wang Y and Wang Z: Erianin alleviates autoimmune myocarditis by suppressing the M1 polarization of macrophages via the NF-κB/NLRP3 signaling pathway. Eur J Pharmacol 990: 177292, 2025.
99. Kang S, Li H, Li M, Zhao Y, Pang J, Dan J and Sheng M: Erianin alleviates doxorubicin-induced cardiotoxicity by activating the Keap1-Nrf2 signaling pathway. Phytomedicine 141: 156684, 2025.
100. Ni J, Chen X, Chen N, Yan Y, Wu Y, Li B, Huang H, Tong H, Liu Y and Dai N: Erianin alleviates LPS-induced acute lung injury via antagonizing P-selectin-mediated neutrophil adhesion function. J Ethnopharmacol 331: 118336, 2024.
101. Klein OR, Ktena YP, Pierce E, Fu HH, Haile A, Liu C and Cooke KR: Defibrotide modulates pulmonary endothelial cell activation and protects against lung inflammation in pre-clinical models of LPS-induced lung injury and idiopathic pneumonia syndrome. Front Immunol 14: 1186422, 2023.
102. Essaidi-Laziosi M, Royston L, Boda B, Pérez-Rodriguez FJ, Piuz I, Hulo N, Kaiser L, Clément S, Huang S, Constant S and Tapparel C: Altered cell function and increased replication of rhinoviruses and EV-D68 in airway epithelia of asthma patients. Front Microbiol 14: 1106945, 2023.
103. Li F, Lu RJ, Zhang YH, Shi P, Ao YY, Cao LF, Zhang YL, Tan WJ and Shen J: Clinical and molecular epidemiology of enterovirus D68 from 2013 to 2020 in Shanghai. Sci Rep 14: 2161, 2024.
104. Aponte-Diaz D, Vogt MR and Cameron CE: An unexpected, ph-sensitive step of the enterovirus D68 lifecycle. mBio 14: e0228123, 2023.
105. Meng X, Yu X, Liu C, Wang Y, Song F, Huan C, Huo W, Zhang S, Li Z, Zhang J, *et al*: Effect of ingredients from Chinese herbs on enterovirus D68 production. Phytother Res 33: 174-186, 2019.
106. Aruoma OI, Grootveld M and Bahorun T: Free radicals in biology and medicine: From inflammation to biotechnology. Biofactors 27: 1-3, 2006.
107. Li Q, Gan X, Zhang M, Zhang G, Li Y and Gao L: Erianin promotes endogenous neurogenesis in traumatic brain injury rats. Sci Rep 14: 4108, 2024.
108. Su C, Liu S, Ma X, Liu J, Liu J, Lei M and Cao Y: The effect and mechanism of erianin on the reversal of oxaliplatin resistance in human colon cancer cells. Cell Biol Int 45: 2420-2428, 2021.
109. Yan W, Zhou Y, Yuan X, Bai P, Tang M, Chen L, Wei H and Yang J: The cytotoxic natural compound erianin binds to colchicine site of β-tubulin and overcomes taxane resistance. Bioorg Chem 150: 107569, 2024.
110. Ouyang P, He X, Yuan ZW, Yin ZQ, Fu H, Lin J, He C, Liang X, Lv C, Shu G, *et al*: Erianin against *Staphylococcus aureus* infection via inhibiting sortase A. Toxins (Basel) 10: 385, 2018.
111. Jia Z, Yue W, Zhang X, Xue B and He J: Erianin alleviates cerebral ischemia-reperfusion injury by inhibiting microglial cell polarization and inflammation via the PI3K/AKT and NF-κB pathways. Int Immunopharmacol 141: 112915, 2024.
112. Yan C, Tian Z, Ruan W, Wu M, Wang W and Liu Z: Erianin isolated from *Dendrobium* huoshanense alleviated neuroinflammation in MPTP-induced Parkinson's disease model via NF-κB/NLRP3 Pathway. J Ethnopharmacol 345: 119620, 2025.
113. Li Q, Gan X, Zhang M, Zhang G, Li Y and Gao L: The influence of erianin on the differentiation of neural stem cells into neurons in vitro. Indian J Pharm Sci 85: 1811, 2023.
114. Wei M, Zhang T, Ouyang H, Huang Z, Lu B, Li J, Xu H, Wang Z and Ji L: Erianin alleviated liver steatosis by enhancing Nrf2-mediated VE-cadherin expression in vascular endothelium. Eur J Pharmacol 950: 175744, 2023.
115. Liu Z, Huang L, Sun L, Nie H, Liang Y, Huang J, Wu F and Hu X: Ecust004 suppresses breast cancer cell growth, invasion, and migration via EMT regulation. Drug Des Devel Ther 15: 3451-3461, 2021.
116. Liu S, Teng F, Lu Y, Zhu Y, Liang X, Wu F, Liu J, Zhou W, Su C and Cao Y: Ethoxy-erianin phosphate inhibits angiogenesis in colorectal cancer by regulating the TMPO-AS1/miR-126-3p/PIK3R2 axis and inactivating the PI3k/AKT signaling pathway. BMC Cancer 24: 1275, 2024.
117. Chen J, Liu J, Xu B, Cao Y, Liang X, Wu F, Shen X, Ma X and Liu J: Ethoxy-erianin phosphate and afatinib synergistically inhibit liver tumor growth and angiogenesis via regulating VEGF and EGFR signaling pathways. Toxicol Appl Pharmacol 438: 115911, 2022.
118. Yuan W, Su C, Yang X, Li Y, Cao Y, Liang X and Liu J: Biological and anti-vascular activity evaluation of ethoxy-erianin phosphate as a vascular disrupting agent. J Cell Biochem 120: 16978-16989, 2019.
119. Deng X, Liu X, Hu B, Liu J, Fu B and Zhang W: Upregulation of MTHFD2 is associated with PD-L1 activation in bladder cancer via the PI3K/AKT pathway. Int J Mol Med 51: 14, 2023.
120. Yang Y, Liu Q, Wang X and Gou S: Design, synthesis, and biological evaluation of histone deacetylase inhibitors derived from erianin and its derivatives. ChemMedChem 18: e202300108, 2023.
121. Lam F, Bradshaw TD, Mao H, Roberts S, Pan Y and Wang S: ZJU-6, a novel derivative of Erianin, shows potent anti-tubulin polymerisation and anti-angiogenic activities. Invest New Drugs 30: 1899-1907, 2012.
122. Gondáš E, Kráľová Trančíková A, Dibdiaková K, Galanda T, Hatok J, Račay P, Dobrota D and Murín R: Immunodetection of pyruvate carboxylase expression in human astrocytomas, glioblastomas, oligodendrogliomas, and meningiomas. Neurochem Res 48: 1728-1736, 2023.
123. Renoult O, Laurent-Blond M, Awada H, Oliver L, Joalland N, Croyal M, Paris F, Gratas C and Pecqueur C: Metabolic profiling of glioblastoma stem cells reveals pyruvate carboxylase as a critical survival factor and potential therapeutic target. Neuro Oncol 26: 1572-1586, 2024.
124. Liu C, Zhou X, Ju H and Zhang Y: Inhibition of pyruvate carboxylase reverses metformin resistance by activating AMPK in pancreatic cancer. Life Sci 327: 121817, 2023.
125. Shi H, Yang J, Qiao Z, Li L, Liu G, Dai Q, Xu L, Jiao W, Zhang G, Wang F, *et al*: Design, synthesis and structure-activity relationship studies on erianin analogues as pyruvate carboxylase inhibitors in hepatocellular carcinoma cells. Org Biomol Chem 21: 7005-7017, 2023.
126. Park S and Hall MN: Metabolic reprogramming in hepatocellular carcinoma: Mechanisms and therapeutic implications. Exp Mol Med 57: 515-523, 2025.
127. Li Y, Li X, Li X, Zhong Y, Ji Y, Yu D, Zhang M, Wen JG, Zhang H, Goscinski MA, *et al*: Retraction: PDHA1 gene knockout in prostate cancer cells results in metabolic reprogramming towards greater glutamine dependence. Oncotarget 16: 790, 2025.
128. Dong S and Li T: Metabolic reprogramming in cancer: Signaling pathways and therapeutic targets. Mol Cancer 25: 60, 2026.

129. Nie H, Wang N, Huang J, Ni Z, Xue K, Song L, Wang M and Wu F: Radiosynthesis and tumor MicroPET/CT imaging of ^{18}F-Fluoroethoxylerianin, an ^{18}F-labeled Erianin analogue. SynOpen 6: 80-85, 2022.
130. Wang Z, Liu W, Li G, Wang J, Zhao B, Huang P and Mei W: Ruthenium(II) complexes coupled by erianin via a flexible carbon chain as a potential stabilizer of c-myc G-quadruplex DNA. Molecules 28: 1529, 2023.
131. Yu HN, Liu YQ, Zheng F, Chen WY and Wei K: Erianin-loaded photo-responsive dendrimer mesoporous silica nanoparticles: exploration of a psoriasis treatment method. Molecules 27: 6328, 2022.
132. Zheng L, Ding Y, Fang S, Yang W, Chen J, Ma J, Wang M, Wang J, Zhang F, Guo X, *et al*: Potentiated calcium carbonate with enhanced calcium overload induction and acid neutralization capabilities to boost chemoimmunotherapy against liver cancer. ACS Nano 18: 27597-27616, 2024.
133. Tian J, Chen K, Zhang Q, Qiu C, Tong H, Huang J, Hao M, Chen J, Zhao W, Wong Y, *et al*: Mechanism of self-assembled celastrol-Erianin nanomedicine for treatment of breast cancer. Chem Eng J 499: 155709, 2024.
134. Mo C, Lu L, Liu D and Wei K: Development of erianin-loaded dendritic mesoporous silica nanospheres with pro-apoptotic effects and enhanced topical delivery. J Nanobiotechnology 18: 55, 2020.
135. Xie H, Feng S, Farag MA, Sun P and Shao P: Synergistic cytotoxicity of erianin, a bisbenzyl in the dietetic Chinese herb *Dendrobium* against breast cancer cells. Food Chem Toxicol 149: 111960, 2021.
136. Yang A, Sun Z, Liu R, Liu X, Zhang Y, Zhou Y, Qiu Y and Zhang X: Transferrin-conjugated erianin-loaded liposomes suppress the growth of liver cancer by modulating oxidative stress. Front Oncol 11: 727605, 2021.
137. Betageri GV, Jenkins SA and Parsons D: Liposome drug delivery systems. 1st edition. CRC Press, 2024.
138. Wang S, Chen Y, Guo J and Huang Q: Liposomes for tumor targeted therapy: A review. Int J Mol Sci 24: 2643, 2023.
139. Liu N, Wang X, Liu H and Zhang C: Identification of the metabolites of erianin in rat and human by liquid chromatography/electrospray ionization tandem mass spectrometry. Rapid Commun Mass Spectrom 34: e8661, 2020.
140. Hannon Barroeta P, O'Sullivan MJ and Zisterer DM: The role of the Nrf2/GSH antioxidant system in cisplatin resistance in malignant rhabdoid tumours. J Cancer Res Clin Oncol 149: 8379-8391, 2023.
141. Georgiou-Siafis SK and Tsiftsoglou AS: The key role of GSH in keeping the redox balance in mammalian cells: Mechanisms and significance of GSH in detoxification via formation of conjugates. Antioxidants (Basel) 12: 1953, 2023.
142. Golubkova A, Leiva T, Snyder K, Schlegel C, Bonvicino SM, Agbaga MP, Brush RS, Hansen JM, Vitiello PF and Hunter CJ: Response of the glutathione (GSH) antioxidant defense system to oxidative injury in necrotizing enterocolitis. Antioxidants (Basel) 12: 1385, 2023.
143. Adejobi OI, Guan J, Yang L, Hu JM, Yu A, Muraguri S and Liu A: Transcriptomic analyses shed light on critical genes associated with bibenzyl biosynthesis in *Dendrobium* officinale. Plants (Basel) 10: 633, 2021.
144. Ta H, Yang YH, Zhu TT, Du NH, Hao Y, Fu J, Xu DD, Xu ZJ, Cheng AX and Lou HX: Catalytic divergence of O-methyltransferases shapes the chemo-diversity of polymethoxylated bibenzyls in *Dendrobium* catenatum. Plant J 120: 29-44, 2024.
145. Xie L, Chen Q, Cheng N, Zhang Y, Ma Y, Zhang Y and Liu K: Integrated metabolomic and transcriptomic analyses of *Dendrobium chrysotoxum* and *D. thyrsiflorum* reveal the biosynthetic pathway from gigantol to erianin. Front Plant Sci 15: 1436560, 2024.
146. Huo D, Liu F, Jiao C, Feng H, Yang C, Cai Q and Xie L: Effects of different extraction solvents on the major chemical compounds and in vitro biological activities of *Dendrobium chrysotoxum* Lindl. Stems. Ind Crops Prod 222: 119678, 2024.
147. Zhang W, Pan X, He J, Lin Y, Zhang F, Guo L and Liu J: A novel strategy for the efficient synthesis of Erianin. Synth Commun 55: 852-861, 2025.
148. Ebrahimi N, Fardi E, Ghaderi H, Palizdar S, Khorram R, Vafadar R, Ghanaatian M, Rezaei-Tazangi F, Baziyar P, Ahmadi A, *et al*: Receptor tyrosine kinase inhibitors in cancer. Cell Mol Life Sci 80: 104, 2023.
149. Sunitha Shyam S, Umesh CS and Saraswati P: Adverse effects of tyrosine kinase inhibitors in cancer therapy: Pathophysiology, mechanisms and clinical management. Signal Transduct Target Ther 8: 262, 2023.
150. Cancemi G, Campo C, Caserta S, Rizzotti I and Mannina D: Single-agent and associated therapies with monoclonal antibodies: What about follicular lymphoma? Cancers (Basel) 17: 1602, 2025.
151. Liao L, Zhang YL, Deng L, Chen C, Ma XY, Andriani L, Yang SY, Hu SY, Zhang FL, Shao ZM and Li DQ: Protein phosphatase 1 subunit PPP1R14B stabilizes STMN1 to promote progression and paclitaxel resistance in triple-negative breast cancer. Cancer Res 83: 471-484, 2023.
152. Harada Y, Nakamura E, Bingham T, Zon LI, Daley GQ, Frelinger A, Eto K and Schlaeger TM: Exposure of Hipsc-derived mature megakaryocytes to vincristine boosts platelet biogenesis in vitro. Blood 142 (Suppl 1): S1292, 2023.