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PHARMACOLOGICAL EFFECTS OF ERIANIN AND ITS DERIVATIVES ON THE TUMOR MICROENVIRONMENT: CURRENT PERSPECTIVES

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Abstract: Cancer development is determined not only by genetic and epigenetic alterations in tumor cells but also by complex interactions with the tumor microenvironment (TME). The TME consists of cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), endothelial cells, immune cells, extracellular matrix, and various signaling molecules. These components play important roles in tumor proliferation, angiogenesis, invasion, metastasis, immune evasion, and the development of drug resistance [2,3]. Erianin is a naturally occurring dibenzyl compound isolated from plants belonging to the genus Dendrobium and has attracted considerable scientific interest in recent years due to its broad pharmacological properties, particularly its antitumor, antiangiogenic, immunomodulatory, and anti-inflammatory activities [1,2]. Available evidence indicates that erianin may affect several signaling pathways, including ROS/JNK, PI3K/AKT, JAK/STAT3, HIF-1α/PD-L1, mTOR, and Wnt/β-catenin [1,2]. In addition, experimental studies have demonstrated that erianin can inhibit angiogenesis, enhance the ability of macrophages to phagocytose tumor cells, and modulate the immune microenvironment [4–7]. The poor water solubility and limited bioavailability of erianin represent major factors restricting its pharmaceutical development and necessitate the development of novel derivatives and drug delivery systems [1,2]. This review analyzes the effects of erianin and its derivatives on the tumor microenvironment, their major molecular mechanisms, potential mechanisms of interaction with CAFs and TAMs, and future pharmacological perspectives.
Keywords: erianin, tumor microenvironment, cancer-associated fibroblasts, tumor-associated macrophages, angiogenesis, immunomodulation, oxidative stress, erianin derivatives.

INTRODUCTION

Cancer is one of the most complex challenges in modern medicine, and its development is regarded as a multifactorial biological process. Conventional anticancer therapy is primarily directed toward blocking malignant cell proliferation, DNA replication, or specific molecular targets. However, the biological environment in which tumor cells reside substantially determines their growth, invasion, metastatic potential, and response to treatment [1,2]. This environment is referred to as the tumor microenvironment (TME**)**. The TME consists not only of tumor cells but also of fibroblasts, macrophages, lymphocytes, endothelial cells, pericytes, extracellular matrix, and numerous cytokines and growth factors [2,3]. In particular, CAFs and TAMs are considered important stromal components that support tumor development. CAFs contribute to tumor progression through extracellular matrix remodeling, angiogenesis, and modulation of immune responses [3,11].TAMs, in turn, play important roles in inflammation, angiogenesis, immunosuppression, metastasis, and intercellular signaling. The interaction between CAFs and TAMs further increases the complexity of the TME, as these cell populations interact with each other through extracellular matrix components and signaling molecules [12,14]. From this perspective, pharmacological modulation of the tumor microenvironment, in addition to targeting tumor cells themselves, is considered a promising therapeutic strategy. Among natural compounds, erianin has attracted particular interest

in recent years. Erianin is a naturally occurring dibenzyl compound isolated from Dendrobium chrysotoxum and other Dendrobium species and has demonstrated antiproliferative, proapoptotic, antiangiogenic, and immunomodulatory effects in various cancer models [1,2].

GENERAL PHARMACOLOGICAL PROPERTIES OF ERIANIN

Erianin is a naturally derived small molecule whose pharmacological activity is associated with multiple biological processes [1,2]. Studies have reported the following effects of erianin:

- antitumor activity;
- antiangiogenic activity;
- anti-inflammatory activity;
- immunomodulatory activity;
- antioxidant or redox-modulating activity;
- antiproliferative activity;
- proapoptotic activity [1,2].

The antitumor mechanisms of erianin are not restricted to a single signaling pathway. Current evidence describes its involvement in pathways such as PI3K/AKT, JAK/STAT3, ERK1/2, JNK, mTOR, HIF-1α/PD-L1, and Wnt/β-catenin [1,2]. For example, in an osteosarcoma model, erianin was shown to increase ROS production and activate the JNK signaling pathway, induce G2/M-phase cell-cycle arrest, and enhance apoptosis and autophagy [8].Another study demonstrated that erianin interacts with pyruvate carboxylase and can modulate Wnt/β-catenin signaling through this metabolic target [9].These findings indicate that the antitumor effects of erianin are not limited to direct cytotoxic activity [1,2].

THE TUMOR MICROENVIRONMENT AND ERIANIN

The TME is not merely a passive “background” for cancer cells. Rather, it is an active biological system that continuously exchanges signals with tumor cells [3,12].The major components of the TME can be summarized as follows:

TME component	Main function
CAFs	ECM synthesis, growth factors, angiogenesis, metastasis
TAMs	Immunosuppression, angiogenesis, phagocytosis, metastasis
Endothelial cells	Angiogenesis
ECM	Mechanical and biochemical signaling
T lymphocytes	Antitumor immune response
Cytokines	Intercellular signaling

TME component	Main function
Hypoxic environment	HIF signaling and angiogenesis

CAFs exhibit a high degree of heterogeneity, and modern single-cell and spatial transcriptomic studies have enabled the identification of their different functional subpopulations [11]. Therefore, rather than simply "eliminating CAFs," reprogramming specific CAF subpopulations or suppressing their pro-tumor functions may represent an important future therapeutic strategy [11].

EFFECTS OF ERIANIN ON ANGIOGENESIS

Angiogenesis is one of the most important processes within the TME. Rapidly growing tumor cells have increased requirements for oxygen and nutrients. Consequently, the expression of VEGF and other angiogenic factors is enhanced.The antiangiogenic properties of erianin represent one of its earliest identified pharmacological effects [15].Studies conducted in 2004 demonstrated that erianin induces rapid tumor-vessel "shutdown" in tumor models, inhibits endothelial cell proliferation and migration, and disrupts capillary tube formation [15].Subsequent studies demonstrated that erianin suppresses indoleamine 2,3-dioxygenase (IDO)-associated angiogenesis and modulates molecular processes associated with JAK2/STAT3, MMP-2/MMP-9, COX-2, HIF-1α, and IL-6 [6].These mechanisms are particularly important from the perspective of the TME because inhibition of angiogenesis may disrupt several components of the following sequence:

hypoxia → angiogenic signaling → formation of new blood vessels → tumor growth/metastasis

A study published in 2026 demonstrated that erianin can normalize aberrant blood vessels in a glioblastoma model, improve T-cell infiltration into tumor tissue, and enhance the efficacy of CAR-T therapy. The authors associated these effects with P4HA1 and the HIF1α/SNAIL/SLUG pathway . These findings suggest that erianin may be investigated not only as a conventional antiangiogenic agent but also as a **modulator capable of rendering the TME more permissive to immunotherapy** [16].

ERIANIN AND CANCER-ASSOCIATED FIBROBLASTS

CAFs are regarded as one of the most active stromal components of the TME.Normal fibroblasts can undergo functional alterations in response to various signals originating from tumor cells. As a result, they may acquire a CAF-like phenotype and exhibit increased expression of α-SMA, FAP, PDGFR, and other markers [3,11].

The major functions of CAFs include:

- synthesis of collagen and other ECM components;
- stimulation of tumor cell migration;
- support of angiogenesis;
- production of cytokines and chemokines;
- modulation of immune-cell activity;
- enhancement of drug resistance [3,11].

The direct experimental evidence regarding the effects of erianin on CAFs remains considerably more limited than the evidence describing its direct effects on tumor cells**.** This aspect should therefore be considered an important scientific gap.At the same time, the effects of erianin on signaling pathways associated with HIF-1α, JAK/STAT3, PI3K/AKT, MAPK, and angiogenesis

suggest the possibility that erianin may modulate CAF biology [1,2]. However, some of these associations should be regarded as indirect or mechanistic hypotheses and require specific experimental validation in CAF models. Therefore, future studies should investigate the effects of erianin on the transition from:

normal fibroblast → CAF-like phenotype

This may involve analysis of the following markers:

- α-SMA/ACTA2;
- FAP;
- PDGFR-β;
- COL1A1;
- fibronectin;
- TGF-β;
- IL-6;
- CXCL12.

ERIANIN AND TUMOR-ASSOCIATED MACROPHAGES

TAMs represent an important population of immune cells within the TME. Although macrophage phenotypes are substantially more complex than a strict "M1/M2" dichotomy, this model remains a useful conceptual framework for mechanistic studies [12]. Within the tumor microenvironment, macrophages may support:

- immunosuppression;
- angiogenesis;
- tumor-cell invasion;
- metastasis;
- ECM remodeling;
- drug resistance [12,14].

One of the most interesting findings concerning the interaction between erianin and macrophages was obtained in a colorectal cancer model. In this study, erianin inhibited β-catenin signaling while simultaneously reducing **CD47** expression in tumor cells. As a result, macrophage-mediated phagocytosis of tumor cells was enhanced [4]. This mechanism is particularly important:

Erianin → CD47↓ → reduced "don't eat me" signal → increased macrophage phagocytosis

Thus, the effects of erianin may extend beyond the tumor cell itself to include the tumor–macrophage interaction [4].

EFFECTS OF ERIANIN ON THE IMMUNE MICROENVIRONMENT

Immune evasion within the TME is an important mechanism contributing to cancer development.The immunomodulatory effects of erianin have been observed in several studies [2,5,7].For example, erianin was shown to suppress HIF-1α synthesis through the mTOR/p70S6K/4EBP1 pathway, reduce PD-L1 expression, and improve the ability of cytotoxic T lymphocytes to eliminate tumor cells [5].In a liver cancer model, erianin altered the levels of multiple cytokines within tumor tissue and modulated processes associated with the immune response [7].These findings indicate that the effects of erianin on the TME can be considered in three major directions:

1. Tumor cells

↓ proliferation
↓ migration
↑ apoptosis/autophagy

2. Tumor vasculature
↓ angiogenesis
↓ aberrant vascularization
↑ vascular normalization
3. Immune/stromal compartment
↑ macrophage phagocytosis
↓ PD-L1-mediated immune escape
potential CAF modulation

MOLECULAR MECHANISMS OF ERIANIN ACTION

The multi-target pharmacological properties of erianin can be summarized through the following major signaling systems:

ROS/JNK

In certain tumor models, erianin increases ROS levels and enhances JNK activation, thereby promoting apoptosis and autophagy [8].

PI3K/AKT/mTOR

This pathway plays a central role in cell proliferation, metabolism, and survival. The effects of erianin on this signaling system have been associated with its antiproliferative and immunomodulatory properties [1,2].

JAK/STAT3

JAK/STAT3 is associated with inflammation, immunosuppression, tumor-cell proliferation, and angiogenesis. Erianin has been shown to reduce JAK2/STAT3 activation in an IDO-associated angiogenesis model [6].

HIF-1α/PD-L1

Under hypoxic conditions, HIF-1α activation contributes to angiogenesis and immune evasion. The effect of erianin on the HIF-1α/PD-L1 axis indicates its potential to modulate the immune microenvironment [5].

Wnt/β-catenin

Erianin can suppress β-catenin signaling and reduce the expression of c-Myc and cyclin D1, which are associated with tumor-cell proliferation [4,9].

ERIANIN DERIVATIVES AND STRUCTURAL MODIFICATION

Although erianin has promising pharmacological potential, one of the major factors limiting its clinical development is its poor water solubility and low bioavailability**.** Rapid metabolism and elimination from the body have also been reported as important pharmacokinetic limitations [1,2].

Therefore, researchers have investigated strategies including:

- chemical modification of the erianin structure;
- development of novel erianin derivatives;
- nanoparticle-based drug delivery;
- combination therapy with other drugs [1,2].

A 2023 medicinal chemistry review specifically discussed structural modification of erianin and structure–activity relationship (SAR) approaches [1]. The goal of these strategies is not only to enhance antitumor activity but also to improve the drug-like properties of erianin through the following sequence:

solubility ↑ → stability ↑ → bioavailability ↑ → selectivity ↑ → therapeutic window ↑ [1,2]

ERIANIN AND CAF–TAM INTERACTION: AN EMERGING RESEARCH DIRECTION

Increasing attention is being paid to the study of CAFs and TAMs not as separate biological components but as a unified **stromal–immune network**.ECM components and signaling molecules

produced by CAFs can influence macrophage phenotypes. In turn, cytokines produced by TAMs can support fibroblast activation. As a result, an interconnected system involving:
CAF ↔ TAM ↔ ECM ↔ Tumor cell is established [12,14].
The effects of erianin on this system have not yet been fully elucidated.From this perspective, the following scientific hypothesis can be proposed: Erianin and its derivatives may remodel the tumor microenvironment not only through direct cytotoxic effects on tumor cells but also by modulating CAF and TAM functions, suppressing angiogenesis, and reducing mechanisms of immune evasion. A tumor cell–fibroblast–macrophage co-culture model may therefore be particularly useful for experimentally investigating this hypothesis.

CHALLENGES IN PHARMACOLOGICAL DEVELOPMENT

Despite the promising biological activity of erianin, several challenges remain in its development as a clinical therapeutic agent.

1) Poor water solubility

The poor aqueous solubility of erianin limits its biological availability [1,2].

2)Pharmacokinetic limitations

Rapid metabolism and elimination may make it difficult to maintain therapeutically effective concentrations [1,2].

3) Complexity of its mechanism of action

Erianin may affect multiple signaling pathways. On the one hand, this demonstrates its potential as a multi-target pharmacological agent; on the other hand, it complicates the identification of a specific molecular target [1,2].

4) Heterogeneity of the TME

Because of the diversity of CAF subpopulations and the plasticity of TAMs, a single universal target may not be equally effective across all tumor types [11,12].

5) Limited clinical evidence

A substantial proportion of the available evidence is derived from cellular and animal models. Therefore, additional pharmacokinetic, toxicological, and clinical studies are required to evaluate the clinical efficacy and safety of erianin [1,2].

FUTURE RESEARCH DIRECTIONS

Future research should focus on the following areas:

1) CAF model

Induction of a CAF-like phenotype in normal fibroblasts using TGF-β and evaluation of the effects of erianin on this process.

2) TAM model

Investigation of the phenotypic and functional effects of erianin in THP-1-derived macrophages or other macrophage models.

3) Co-culture

Development of a three-component model consisting of tumor cells, fibroblasts, and macrophages.

4) Molecular markers

CAF:

- α-SMA
- FAP
- COL1A1
- PDGFR-β
- TGF-β

TAM:
- CD68
- CD163
- CD206
- HLA-DR
- iNOS

TME:
- IL-6
- IL-10
- TGF-β
- VEGF
- HIF-1α
- MMP-2
- MMP-9

5) Signaling pathways
- PI3K/AKT/mTOR
- JAK/STAT3
- HIF-1α
- NF-κB
- Wnt/β-catenin
- JNK
- MAPK

6) Multi-omics

Transcriptomic, proteomic, and metabolomic approaches may be used to investigate the comprehensive remodeling of the TME induced by erianin.

CONCLUSION

Erianin is a naturally occurring bioactive compound derived from plants of the genus Dendrobium and possesses broad pharmacological properties. Current evidence indicates that erianin can suppress cell proliferation, migration, and invasion in various tumor models and can activate apoptosis and other mechanisms of cell death. Its effects on signaling pathways such as ROS/JNK, PI3K/AKT/mTOR, JAK/STAT3, HIF-1α/PD-L1, and Wnt/β-catenin demonstrate its multi-target pharmacological properties [1,2,4–9]. Of particular interest is the potential effect of erianin on the tumor microenvironment. Its ability to inhibit angiogenesis, modulate immune-evasion mechanisms, and enhance macrophage-mediated phagocytosis of tumor cells supports the concept of targeting the TME as a therapeutic strategy [4–7,15,16]. However, the direct and interconnected mechanisms through which erianin affects CAFs and TAMs remain insufficiently characterized**.** This represents an important scientific gap for future research. The poor aqueous solubility, limited bioavailability, and rapid metabolism of erianin remain major challenges for its pharmaceutical development. Therefore, the development of novel erianin derivatives, nanodrug delivery systems, and combination therapies represents an important area of research [1,2]. Overall, the available evidence indicates that erianin should be investigated not only as a natural compound acting directly on cancer cells but also as a potential TME-targeting agent capable of modulating interactions among tumor cells, CAFs, TAMs, endothelial cells, and the immune system.

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