Eupatilin unveiled: An in-depth exploration of research advancements and clinical therapeutic prospects

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ABSTRACT

Eupatilin, a flavonoid found in Artemisia argyi (Compositae) leaves, exhibits robust anti-inflammatory, antioxidant, and anti-tumor properties. Numerous investigations have demonstrated remarkable efficacy of eupatilin across various disease models, spanning digestive, respiratory, nervous, and dermatological conditions. This review aims to provide an overview of recent studies elucidating the mechanistic actions of eupatilin across a spectrum of disease models and evaluate its clinical applicability. The findings herein provide valuable insights for advancing the study of novel Traditional Chinese Medicine compounds and their clinical utilization.

Key words: anti-inflammatory properties, antitumor properties, clinical trials, eupatilin, immunoregulation; pharmacological activities

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INTRODUCTION

Natural products (NPs) continue to exhibit value in medicine, serving not only as therapeutic agents but also as a pivotal source of innovative drug candidates.[1] The term "natural products" encompasses chemical compounds derived from living organisms, including plants, microorganisms, and marine life.[2] The historical utilization of plants for medicinal purposes has yielded numerous significant and effective drugs, spanning from early examples like quinine and morphine to more contemporary drugs such as paclitaxel (taxol), camptothecin and artemisinin.[3] In the context of modern medicine, there is a prevailing trend towards the extraction and pharmacological validation of active monomers from NPs, such as those found in traditional Chinese medicine, which plays a pivotal role in its continued advancement.[4,5]

Artemisia argyi (mugwort), a traditional Chinese herb with historical references dating back to the 11th-6th century B. C. in the Book of Songs, has been used for millennia in practices like moxibustion and the treatment of conditions including eczema, diarrhea, hemostasis, and menstruation-related symptoms.[6] Eupatilin, a main polyphenolic compound of Artemisia argyi, has garnered increasing attention from researchers since its isolation. Eupatilin is a lipophilic flavonoid constituent of the plant, appearing as a yellow powder with the molecular formula C18H16O7. Its chemical structure was first discovered in 1969[7] (Figure 1).

Eupatilin comprises various pharmaceutical formulations and derivatives. For instance,

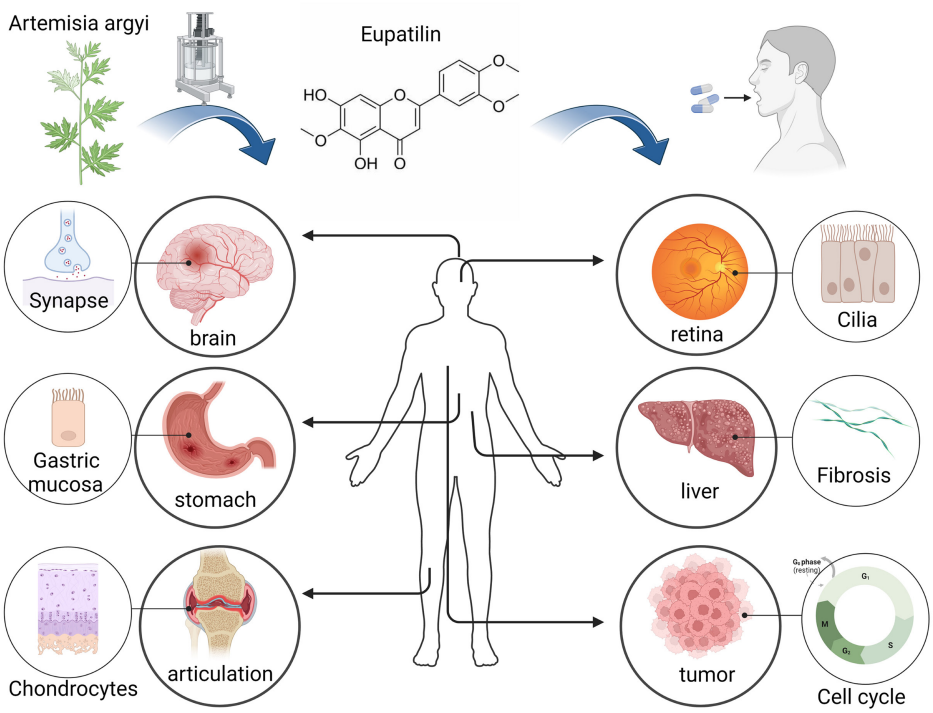

Figure 1: The therapeutic target of eupatilin. Eupatilin, derived from plants like mugwort, exhibits therapeutic potential across various organ systems, including the brain, stomach, joints, eyes, liver, and tumors. Its pharmacological actions encompass anti-inflammatory, antioxidant, and anti-proliferative effects, targeting specific cytokines and pathways associated with these conditions. (Created with Biorender. com, with permission.)

DA-9601 (Stillen®; Dong-A ST Co., Seoul, Korea), an immediate-release product derived from Artemisia asiatica, is employed to manage erosive gastritis.[8,9] The DA-5204 tablet (Stillen 2X®; Dong-A ST Co.) contains 90 mg of Artemisia asiatica extract derived from a 95% ethanol concentration, a novel formulation designed for extended intragastric retention of the active ingredient and is administered twice daily instead of thrice daily.[9] The efficacy of both DA-9601 and DA-5204 in treating erosive gastritis is comparable.[9,10] DA-6034, a synthetic derivative of eupatilin, exhibits high tolerability and minimal absorption in healthy volunteers. The localized contact with the gastrointestinal tract may render DA-6034 a promising option for non-systemic treatment of Irritable Bowel Disorder.[11]

Eupatilin exhibits versatility in various significant pharmacological activities, with its anti-inflammatory properties being of particular interest (Figure 2). Currently, most marketed drugs featuring eupatilin are primarily prescribed for management of inflammatory gastrointestinal diseases.[8–12] Furthermore, its confirmed roles in autophagy, cell cycle arrest, and apoptosis promotion have also sparked interest in its potential anti-tumor applications.[13,14] Additionally, for rare phenotypes such as ciliopathy-related phenotypes, eupatilin shows promising therapeutic potential.[15] In this review article, we will comprehensively assess the mechanisms of action, clinical research, and the potential applications of eupatilin.

OVERVIEW OF ANTI-INFLAMMATORY EFFECTS AND MECHANISMS OF EUPATILIN

Eupatilin exerts potent anti-inflammatory effects primarily through modulation of the NF-κB pathway alongside the regulation of various signaling pathways and targets, including JAK2/STAT3, TLR4/MyD88, MAPK, and PI3K/AKT (Figure 2, Table 1). By inhibiting the activation of inflammatory pathways and reducing the production of inflammatory factors, it produces a broad, sustained and strong anti-inflammatory activity. These effects are achieved without substantially impacting physiological homeostasis, indicating a high safety profile.

Eupatilin demonstrates broad-spectrum anti-inflammatory effect in various anatomical regions, including the gastrointestinal tract, lungs, brain, skin, bones, and joints (Figure 1). It serves as the key component in "Stillen®", a gastroprotective medication manufactured in Korea, recognized for its potent inflammation-reducing and cytoprotective attributes.[12] Notably, eupatilin

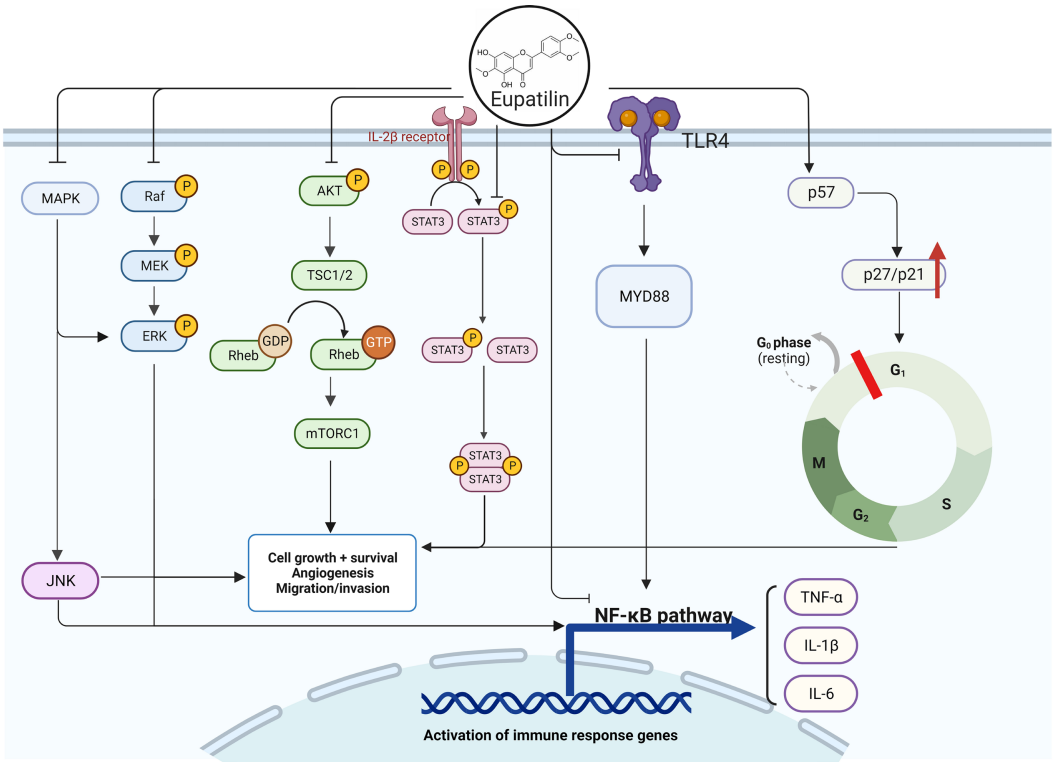

Figure 2: The main mechanism of action of eupatilin. The anti-inflammatory effects of eupatilin primarily involve the inhibition of the NF-κB pathway, exerting a direct impact on NF-κB or indirectly suppressing NF-κB and inflammatory cytokines (IL-1β, IL-6, TNF-α) *via* TLR4, MAPK, and ERK cascade signaling. Simultaneously, eupatilin induces cell cycle arrest through PI3K-AKT, STAT3, p57, p27, p21 and other mechanisms to inhibit the growth and metastasis of cancer cells, showing anti-cancer properties. (Created with Biorender.com, with permission.)

demonstrates exceptional efficacy in inhibiting contraction of gastrointestinal smooth muscle and increasing the secretion of mucus and prostaglandins (PG) in the gastric mucosa, making it a promising candidate for the development of gastrointestinal therapeutics.[9–12] Eupatilin exhibits potent and long-lasting anti-inflammatory effects, significantly impacting acute and chronic respiratory inflammation. It effectively suppresses inflammatory pathway activation and secretion of inflammatory factors in airway smooth muscle and bronchial epithelial cells, alleviating airway remodeling and allergic responses.[16,17] As a potential neuroprotective agent, eupatilin regulates microglia, glutamatergic synaptic protein and TLR4, and has shown great therapeutic potential especially in ischemic stroke, cerebral hemorrhage, acute and chronic brain injury, and Parkinson's disease.[18–21] As a small molecule agonist of sestrin2, eupatilin promotes the phosphorylation of PI3K/AKT pathway, the proliferation and migration of keratinocytes and re-epithelialization through sestrin2, which plays a key role in the wound repair of deep second-degree burn.[22] In addition, eupatilin inhibits NF-κB and MAPK/AP-1 pathway through PPARα, thus inhibiting MMP-2/-9 expression induced by TNFα, which plays a role in preventing skin aging.[23] Eupatilin exhibits diverse effects on cartilage, including anti-inflammatory action, inhibition of apoptosis and promotion of autophagy, and promotion of chondrogenesis, warranting further investigation[24–26] (Figure 2).

THE ROLE OF EUPATILIN IN GASTROINTESTINAL INFLAMMATION

In the digestive system, eupatilin mainly targets mucosal cells and protects gastrointestinal mucosa by inhibiting NF-κB pathway, reducing the expression of inflammatory factors and activating inflammatory pathways. Also, eupatilin increase the expression of mucosal and gastrointestinal protective factors. For example, Paik *et al.* demonstrated that eupatilin effectively inhibits PKD1/NF-κB activation and the nuclear translocation of NF-κB in pancreatic acinocytes. This results in the downregulation of pancreatitis-induced IL-1β, IL-6, CC chemokine ligands 2 and 5, while upregulating the expression of anti-inflammatory factors IL-4 and IL-10. This consequently leads to a reduction in inflammation levels in pancreatitis models.[27] Du *et al.* showed that eupatilin could increase the levels of superoxide dismutase, glutathione and IL-10, and decrease the contents of malondialdehyde, tumor necrosis factor-α, IL-1β and IL-6. Significantly down-regulated the

Table 1: Anti-inflammatory mechanism of eupatilin

Diseases/Phenotype	Experimental model	Mechanisms/ Results	References
Pancreatitis	Pancreatic acinar cells *In vitro*	↓ PKD1/NF-κB ,IL-1β, IL-6, CCL2,CCL5 ↑ IL-4 ,IL-10	Paik *et al.*,[27]
Ulcerative colitis	Intestinal epithelial (NCM460) cells *In vitro* colitis mice *in vivo*	↓ NOX4 ↑ AMPK ameliorated the symptoms and pathologic changes (AMPK pharmacological inhibitor)	Zhou *et al.*,[28]
Esophagitis	Feline esophageal epithelial cells (EEC) *In vitro*	↑ HO-1,PI3K/Akt, ERK,Nrf2 translocation	Song *et al.*,[29]
		↑ HSP27,HSP70	Kim *et al.*,[30]
Acute Lung Injury	Rats (LPS-induced) *in vivo*	↓ SP-A, SP-D, IL-6,TNF-α,MCP-1 ↑ PPAR-α	Liu *et al.*,[16]
Asthma	Airway smooth muscle cells (ASMCs) *In vitro*	↓ TGF-β1,NF-κB,STAT3,AKT,ECM I,Coll I ↑ α-SMA,	Li *et al.*,[31]
Asthma	Asthmatic mice(OVA-induced) *in vivo*	↓ NF-κB,MAPK,NO,IL-6,ROS ↓ Nrf2	Bai *et al.*,[17]
Asthma	Guinea pig lung mast cells *In vitro*	↓ Syk tyrosine,Ca($^{2+}$) influx	Kim *et al.*,[32]
Asthma	Human bronchial epithelial cell line (BEAS-2B) *In vitro*	↓ MAPK,IKK,NF-κB,eotaxin-1 (CCL11)	Jeon *et al.*,[33]
Asthma	Human bronchial epithelial cell line (BEAS-2B) *In vitro*	↓ IκBα,NF-κB,phosphorylation of Akt	Jung *et al.*,[34]
Cerebral ischemia	Mice(induced in mice by bilateral common carotid artery occlusion) *in vivo*	↑ Akt phosphorylation	Cai *et al.*,[35]
Cerebral ischemia	BV2 microglia *In vitro*	↓ IKKα/β phosphorylation, IκBα phosphorylation, and IκBα degradation	Sapkota *et al.*,[36]
Glutamate neurotoxicity	Rats(Glutamate Excitotoxicity Induced by KA) *in vivo*	↓ P/Q-type Ca^{2+} channels,synapsin I phosphorylation	Lu *et al.*,[18]
Intracranial hemorrhage	Erythrocyte lysis stimulation (ELS) to induce mouse microglia BV2 *In vitro*	↓ TLR4,MyD88	Fei *et al.*,[19]
Subarachnoid hemorrhage	BV2 microglia *In vitro* Rats(intravascular perforation) *in vivo*	↓ IL-1β,IL-6,TNF-α,MyD88,TLR4,and p-NF-κB p65	Hong *et al.*,[20]
Parkinson	Mice(MPTP) *in vivo*	↓ IκBα, IκBα,cell apoptosis ↑ Akt,GSK-3βphosphorylation	Zhang *et al.*,[21]
Deep second-degree burn	Mice (mouse model of deep second degree burn) *in vivo*	↑ sestrin2,PI3K/AKT phosphorylation	Wang *et al.*,[22]
Acne	Human SZ95 sebocytes *In vitro*	↓ Akt,PPARγ,SREBP-1 phosphorylation	Lee *et al.*,[37]
Dermatitis	HaCaT human epidermal keratinocytes *In vitro*	↓ NF-κB ,MAPK/AP-1,MMP-2/-9 ↑ PPARα	Jung *et al.*,[23]
Psoriasis	HaCaT cells *In vitro* Mice(Imiquimod) *in vivo*	↓ TNF-α,IL-6,IL-23,IL-17,p38 MAPK/ NF-κB	Bai *et al.*,[38]
Osteoarthritis	Chondrocytes of rats(chloroquine) *in vivo*	↓ mTOR ↑ sestrin2	Lou *et al.*,[24]
Osteoarthritis	Collagen-induced arthritis (CIA) mice *in vivo* human rheumatoid synoviocytes *In vitro*	↓ IL-6 , IL-1β mRNAs	Kim *et al.*,[25]
Osteoarthritis	Rats(monosodium iodoacetate) *in vivo* human OA chondrocytes *In vitro*	↓ IL-1β,IL-6,iNOS;MMP-3,MMP-13,ADAMTS-5 mRNA,JNK phosphorylation	Jeong *et al.*,[39]
Osteoporosis	Rat cartilage cells *In vitro*	c-Fos,NFATc1 transcriptional inhibition	Kim *et al.*,[40]
Fracture Healing	MC3T3-E1 cells *In vitro*	↓ NF-κB ↑ Hsa_circ_0045714,PI3K/AKT	Sun *et al.*,[26]

expression of NF-κB signal pathway, thus reducing the inflammatory response.[28]

Moreover, eupatilin exhibits a pronounced cytoprotective effect on mucous membranes. Zhou *et al.* reported that eupatilin significantly stabilizes colonic epithelial cells by downregulating the overexpression of tight junction proteins and NOX4. Additionally, it promotes AMPK activation in damaged intestinal epithelial cells stimulated by TNF-α. These actions contribute to improved colitis in mice by inhibiting inflammation and preserving intestinal integrity.[29] The mucosal protection provided by eupatilin is particularly effective in cases of mucosal injury resulting from non-steroidal anti-inflammatory drugs (NSAIDs). Song *et al.* confirmed that heme oxygenase-1 (HO-1) inhibitor ZnPP inhibited eupatilin-induced HO-1 activity and showed the protective effect of eupatilin on indomethacin-induced cell injury. HO-1 is partly responsible for the eupatilin-mediated protective effect of esophageal epithelial cells on indomethacin through extracellular signal-regulated kinases (ERKs) and PI3K/Akt pathways and Nrf2 translocation.[30] Furthermore, Kim *et al.* identified that eupatilin upregulates heat shock proteins HSP27 and HSP70 to protect cultured cat food duct epithelial cells from indomethacin-induced damage. They characterized the signaling pathways regulated by HSP27 and HSP70, which may involve the activation of PTK, PKC, PLC, p38MAPK, JNKs, and PI3K.[31] Eupatilin could serve as an alternative or complementary option to NSAIDs to prevent NSAID-induced mucosal damage.

THE ROLE OF EUPATILIN IN RESPIRATORY INFLAMMATION

Eupatilin has demonstrated remarkable efficacy in the management of acute lung injury, acute and chronic respiratory inflammation, such as asthma. For instance, Liu *et al.* reported that eupatilin reduces levels of surfactant proteins SP-A and SP-D, as well as inflammatory factors IL-6, TNF-α, and monocyte chemotactic protein MCP-1, and reversed the production of nitric oxide (NO), malondialdehyde (MDA), lactate dehydrogenase (LDH), and superoxide dismutase (SOD) activity induced by oxidative stress in rat models of acute lung injury. This effect may be closely associated with the activation of PPAR-α, thereby mitigating lung injury.[16] Bai *et al.* demonstrated that eupatilin alleviates ovalbumin-induced asthma in mice by modulating NF-κB, MAPK, and Nrf2 signaling pathways. *In vivo*, eupatilin inhibits the activation of NF-κB and MAPK pathways and increases the expression of Nrf2. *In vitro*, eupatilin significantly reduces LPS-stimulated production of NO, IL-6, and reactive oxygen species (ROS).[17] Li *et al* revealed that eupatilin inhibits transforming growth factor β1 (TGF-β1)-induced proliferation and migration of airway smooth muscle cells (ASMCs). Exposure of ASMCs to eupatilin increased the expression of contractile markers smooth muscle α-actin (α-SMA) and myocardin, whereas the expression of extracellular matrix (ECM) proteins collagen type I (CollI) and fibronectin was reduced. Furthermore, eupatilin treatment reversed the activation of NF-κB, signal transducer and activator of transcription 3 (STAT3) and AKT pathways in ASMCs induced by TGF-β1. These findings suggest that eupatilin may alleviate airway remodeling by regulating the phenotypic plasticity of ASMCs.[32] Kim *et al.* found that eupatilin initially inhibits Syk kinase and subsequently blocks multiple downstream signaling pathways and Ca^{2+} influx during mast cell activation triggered by specific antigen-antibody responses, thereby ameliorating allergic and inflammatory responses.[33] Moreover, Jeon *et al.* observed that eupatilin suppresses the signaling of MAPK, IKK, NF-κB, and eotaxin-1 in bronchial epithelial cells, consequently inhibiting eosinophilic migration and reducing asthma-related inflammation.[34] Jung *et al.* demonstrated that eupatilin significantly inhibits the expression of intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) in a dose-dependent manner, while inhibiting the activation of IκBα and nuclear factor-κB signaling and the phosphorylation of Akt action ultimately inhibits the adhesion of inflammatory cells to epithelial cells.[35] In conclusion, eupatilin may act as an anti-inflammatory agent exerting a significant therapeutic effect in the treatment of asthma. Eupatilin plays a crucial role in preventing inflammatory cell infiltration and reducing airway remodeling by providing anti-inflammatory and antioxidant properties, offering a valuable adjunctive treatment option for asthma patients.

THE ROLE OF EUPATILIN IN NERVOUS SYSTEM INFLAMMATION

Eupatilin exerts its neuroprotective effect mainly by regulating the inflammatory pathways of neurons and microglia, such as NF-κB, TLR4 and AKT. Cai *et al.* reported that eupatilin mitigates neuronal damage resulting from global cerebral ischemia, with its neuroprotective effect potentially attributed to increased Akt phosphorylation.[36] Sapkota *et al.* observed that eupatilin inhibits NF-κB signaling in ischemic brain by suppressing phosphorylation and degradation of IKKα/β and IκBα, thus reducing microglial activation and countering focal cerebral ischemia.[37] Lu *et al.* demonstrated that eupatilin reduces glutamate exocytosis in cerebral cortex synaptosomes by diminishing phosphorylation of P/Q-type Ca2+ channels and synapsin protein I, thereby alleviating glutamate excitatory toxicity, eupatilin may be considered as a potential therapeutic agent in the treatment of brain

damage associated with glutamate excitotoxicity.[18] Fei *et al.* determined the therapeutic potential of eupatilin on inflammation caused by intracerebral hemorrhage, indicating that TLR4/MyD88 pathway is involved in anti-inflammation and reducing cell edema and death, which provides hope for the improvement and prognosis of brain edema caused by inflammation in intracerebral hemorrhage.[19] Huang *et al.* further elucidated the role of eupatilin in improving early brain injury induced by subarachnoid hemorrhage in a rat model by modulating the TLR4/MyD88/NF-κB pathway.[20] Additionally, Zhang *et al.* revealed that eupatilin improved the Parkinson's disease (PD) behavioral disorders caused by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and inhibited the expression of inflammatory factors TNF-α, IL-1β, and IL-6. Further research results showed that Eupatilin eliminated the MPTP-induced downregulation of IκBα expression and the accumulation of p65 in the nuclear compartment, restored the phosphorylation of Akt and GSK-3β, and played an inhibitory role in inflammation and apoptosis.[21]

THE ROLE OF EUPATILIN IN CUTANEOUS INFLAMMATION

Eupatilin demonstrates efficacy in skin inflammation-related diseases. Wang *et al.* reported that eupatilin activates Sestrin2 (SESN2), facilitating re-epithelialization of burn wounds through the PI3K/AKT pathway and promoting deep second-degree burn wound healing. Notably, eupatilin is the most specific and effective SESN2 activator, making it a promising compound for deep second-degree burn wound treatment.[22] Acne, characterized by inflammation of the hair follicle sebaceous gland unit, is another condition where eupatilin shows promise. Lee *et al.* revealed that eupatilin inhibits IGF-I-induced sebum cell adipogenesis by suppressing Akt phosphorylation, peroxisome proliferator-activated receptor γ (PPARγ), and mature SREBP-1. Furthermore, eupatilin downregulates TNF-α, IL-6, and IL-8 mRNA expression in sebum cells at the transcriptional level, suggesting its potential as an acne treatment.[38] Matrix metalloproteinases (MMPs) are key proteins in skin damage and aging. Jung *et al.* demonstrated that eupatilin inhibits NF-κB and MAPK/AP-1 pathway through PPARα, thus inhibiting MMP-2/-9 expression induced by TNF-α and preventing skin aging.[23] Bai *et al.* revealed that eupatilin inhibits mouse keratinocyte proliferation via the p38MAPK/NF-κB signaling pathway. In a psoriasis model, eupatilin significantly reduces skin erythema, scales and thickness scores, improves skin histopathological lesions, and reduces serum levels of TNF-α, IL-6, IL-23, and IL-17, indicating its therapeutic potential.[39]

THE ROLE OF EUPATILIN IN OSTEOARTHRITIS

Cartilage degradation is a hallmark of osteoarthritis (OA). Increasing evidence links chondrocyte apoptosis and autophagy to cartilage degeneration. Lou *et al.* demonstrated that eupatilin protects chondrocytes by suppressing IL-1β-induced apoptosis *via* Sestrin2-dependent autophagy.[24] Kim *et al.* also observed the ability of eupatilin to reduce inflammatory cytokine expression, inhibit osteoclast differentiation, and ameliorate OA symptoms.[25] Jeong *et al.* reported the role of eupatilin in reducing IL-1β, IL-6, nitric oxide synthase (iNOS) expression, and phosphorylated JNK in cartilage. Eupatilin exhibits potential as an OA therapeutic by mitigating oxidative damage and enhancing extracellular matrix production in chondrocytes.[40] Furthermore, eupatilin potently inhibited RANKL-induced osteoclast formation, accompanied by suppressed phosphorylation of Akt, GSK3β, ERK, and IκB, and downregulation of c-Fos and NFATc1. It also disrupts the actin ring in multinucleated osteoclasts, halting bone resorption and inducing a fibroblast-like transformation. In LPS-induced osteoporotic mice and ovariectomized (OVX) mice, Eupatilin prevents bone loss and shows osteoprotective effects, highlighting its potential as a multifaceted therapeutic intervention for osteoporosis.[41] The anti-inflammatory effect of eupatilin also supports fracture healing, stimulating NF-κB blockage, PI3K/AKT activation, and Hsa_circ_0045714 production, enhancing osteoblast survival, proliferation, and migration.[26] The multifaceted effects of eupatilin on cartilage include inflammation inhibition, apoptosis and autophagy suppression, and chondrogenesis promotion, warranting further investigation.

OVERVIEW OF ANTI-TUMOR EFFECTS AND MECHANISMS OF EUPATILIN

Eupatilin elicits anti-tumor effects predominantly through inducing cell cycle arrest, suppressing proliferation and migration, inhibiting angiogenesis, and promoting apoptosis in tumor cells. Through a multifaceted targeting strategy, eupatilin selectively acts on key molecular components involved in vascular endothelial growth factor (VEGF), cyclin, ERK, among others, effectively attenuating tumor progression at various stages. The implicated pathways align with those associated with inflammatory conditions, including NF-κB/PI3K/AKT/MAPK (Figure 2, Table 2). Notably, the anti-tumor investigations of eupatilin primarily examine gastrointestinal malignancies, with a specific focus on stomach and colon cancers. Additionally, research has explored its effects on ovarian cancer, endometrial cancer, prostate cancer, gliomas, and various other tumor types.

These findings suggest that eupatilin exhibits a broad-spectrum antitumor activity, indicating its potential as an adjunct therapeutic option for diverse malignancies.

THE ROLE OF EUPATILIN IN DIGESTIVE SYSTEM TUMORS

Eupatilin exhibits potential in the treatment of gastrointestinal malignancies including gastric, liver, and esophageal cancers. Research by Kim *et al.* demonstrated that eupatilin effectively induces apoptosis in gastric cancer (AGS) cells, as evidenced by a reduction in the Bax/Bcl-2 ratio, activation of caspase-3, and cleavage of poly (ADP-ribose) polymerase (PARP). Additionally, it perturbs the mitochondrial transmembrane potential ($\Delta\Psi m$), further indicating its apoptotic action. The compound also upregulates the expression of tumor suppressor proteins p53 and p21, while concurrently inhibiting the activation of extracellular ERK1/2 and Akt, which are integral to cell survival pathways. Collectively, these findings underscore the therapeutic potential of Eupatilin in gastric cancer treatment by modulating both apoptotic and cell survival signaling pathways.[42] Additionally, Choi *et al.* revealed that the anti-cancer effects of eupatilin extend beyond apoptosis, as it induces G(1) phase cell cycle arrest in AGS cells *via* ERK cascade signaling. This results in morphological changes in AGS cells, including increased cell size, particle size, and mitochondrial mass, along with the promotion of cell differentiation and cell cycle alteration.[43] Park *et al.* found that eupatilin inhibits MKN-1 gastric cancer cell proliferation by activating caspase-3 and suppresses the metastatic potential of gastric cancer cells by downregulating NF-κB activity and then reducing pro-inflammatory cytokine-mediated MMP expression.[44] Cheong *et al.* also discovered that Eupatilin inhibits gastric cancer cell growth by blocking STAT3-mediated VEGF expression, thereby disrupting the signaling pathways essential for tumor angiogenesis and proliferation.[45] This angiogenesis and tumor metastasis inhibition capability extends to liver cancer, with studies showing the capacity of eupatilin to reduce MMP-2 and VEGF-mediated metastasis in hepatocellular carcinoma.[46] In other digestive system tumor studies, eupatilin is highlighted for its anti-proliferative properties, stagnant cell cycle regulation, and pro-apoptotic mechanisms. For instance, Wang *et al.* discovered that eupatilin treatment in a human esophageal cancer TE1 xenograft mouse model reduces tumor volume and inhibits phosphorylation of Akt and ERK1/2 in tumor tissues, suggesting that eupatilin may play a role in suppressing TE1 cell proliferation through Akt/GSK3β and MAPK/ERK signaling pathways.[47] Park *et al.* found that EPT suppresses pancreatic cancer cell viability by inhibiting glucose uptake, activating AMPK, and inducing cell cycle arrest.[48] Similarly, Lee *et al.* demonstrated that eupatilin inhibited colon cancer cell viability, induced apoptosis with mitochondrial depolarization, and triggered oxidative stress. It modulated proteins involved in endoplasmic reticulum stress and autophagy and targets the PI3K/AKT and MAPK pathways. Additionally, eupatilin synergizes with 5-fluorouracil (5-FU) in 5-FU-resistant HCT116 cells, suggesting its potential as an adjuvant to potentiate the effects of traditional chemotherapy in colon cancer.[49] In conclusion, eupatilin demonstrates a wide range of antitumor activities, including apoptosis promotion, differentiation induction, anti-proliferation, and cell cycle regulation.

THE ROLE OF EUPATILIN IN GYNECOLOGICAL TUMORS

Eupatilin showed potential to treat a variety of gynecological tumors, including cervical cancer, endometrial cancer and ovarian cancer. Wu *et al.* illustrated that eupatilin regulates cervical cancer proliferation and cell cycle progression by modulating the hedgehog (Hh) signaling pathway.[50] Cho *et al.* revealed that eupatilin upregulates p21 expression by inhibiting mutant p53 and activating the ATM/Chk2/Cdc25C/Cdc2 checkpoint pathway, leading to G2/M phase cell cycle arrest and inhibition of human endometrial cancer cell growth.[51] Lee *et al.* demonstrated that eupatilin enhances the therapeutic effects of conventional chemotherapeutic agents on ovarian cancer cells. The therapeutic effect of eupatilin is associated with caspase activation, cell cycle arrest, increased production of ROS, calcium influx, disruption of the endoplasmic reticulum (ER)-mitochondrial axis, SERPINB11 inhibition, and downregulation of phosphoinositol, ultimately promoting apoptosis in ovarian cancer cells.[52] Eupatilin downregulates key cell cycle regulators, including cyclin D1, cyclin B1, Cdk2, and Cdc2, leading to cell cycle arrest and inhibiting the proliferation of H-ras-transformed breast epithelial (MCF10A-ras) cells related to ERK1/2 pathway inhibition.[53] Research on the application of eupatilin in gynecological tumors primarily centers on its ability to induce cell cycle arrest, resulting in decreased cell proliferation and increased apoptosis.

THE ROLE OF EUPATILIN IN URINARY SYSTEM TUMORS

Eupatilin has a significant anti-tumor effect on prostate cancer cells. By up-regulating caspase3, Bax and cytochrome c, it reduces the viability of prostate cancer cells, induces apoptosis, and regulates the cell cycle by up-regulating p53, p21 and p27, making the cell cycle stagnant in G1 phase. In addition, eupatilin inhibits cell migration and invasion by down-regulating Twist, Slug and MMP-2-7, while increasing the expression of tumor suppressor PTEN and reducing

Table 2: Anticancer mechanism of eupatilin

Diseases/Phenotype	Experimental model	Mechanisms/ Results	References
Gastric cancer	Human promyelocytic leukemia (HL-60) cells *in vitro*	Apoptosis-promoting ↓ Bax/Bcl-2,ERK1/2,Akt ↑ p53,p21	Kim *et al.*,[41]
Gastric cancer	Human gastric epithelial AGS cells *in vitro*	Cell cycle arrest ↑ TFF1,p21 ZO-1 redistribution,ERK cascades	Choi *et al.*,[42]
Gastric cancer	Human gastric cancer cell line, MKN-1 *in vitro*	Anti-metastatic ↑ caspase-3	Park *et al.*,[43]
Gastric cancer	MKN45 cells *in vitro*	Inhibition of angiogenesis ↓ VEGF, ARNT and STAT3	Cheong *et al.*,[44]
Hepatocellular Carcinoma	Human umbilical vein vascular endothelial cells (HUVECs) *in vitro*	Anti-metastatic ↓ HIF-α,VEGF,phosphorylated Akt expression,MMP2	Park *et al.*,[45]
Hepatocellular Carcinoma	Human hepatoma SMMC-7721 cells *in vitro*	Inhibition of tumor proliferation ↓ p53,Topo II,bcl-2	Liu *et al.*,[46]
Esophageal Cancer	Human esophageal cancer cells *in vitro*	Cell cycle arrest Inhibition of tumor proliferation ↓ phosphorylation of Akt and ERK1/2	Wang *et al.*,[47]
Pancreatic Cancer	MIA-PaCa2 cells *in vitro*	Cell cycle arrest ↓ glucose uptake,Tap73 ↑ AMPK	Park *et al.*,[48]
Colon Cancer	Cancer cell lines, namely HCT116 and HT29 *in vitro*	Apoptosis-promoting ↓ PI3K/AKT ↑ MAPK,The anticancer effect of 5-fluorouracil	Lee *et al.*,[49]
Cervical Cancer	Cervical cancer cell lines (C4-1, HeLa, Caski, and Siha) and Ect1/E6E7 cells *in vitro*	Apoptosis-promoting Cell cycle arrest ↓ hedgehog pathway(PTCH, SMO, GLI)	Wu *et al.*,[50]
Endometrial Cancer	Human endometrial cancer cells *in vitro*	Cell cycle arrest ↓ mutant p53 ↑ p21	Cho *et al.*,[51]
Ovarian Cancer	Ovarian cancer cells *in vitro*	Apoptosis-promoting ↓ SERPINB11	Lee *et al.*,[52]
Breast Cancer	H-ras-transformed human breast epithelial (MCF10A-ras) cells *in vitro*	Cell cycle arrest ↓ cyclin D1, cyclin B1, Cdk2 and Cdc2	Kim *et al.*,[53]
Prostate Cancer	Human prostate cancer PC3 and LNCaP cells *in vitro*	Anti-metastatic Inhibition of tumor proliferation ↓ NF-κB ↑ PTEN	Serttas *et al.*,[54]
Renal Cancer	786-O cell *in vitro*	Apoptosis-promoting anti-metastatic ↓ miR-21	Zhong *et al.*,[55]
Renal Cancer	786-O cell *in vitro*	Apoptosis-promoting ↓ PI3K/AKT ↑ MAPK	Zhong *et al.*,[56]
Glioma	Glioma cell *in vitro*	Cell cycle arrest anti-metastatic Inhibition of tumor proliferation ↓ P-LIMK/cofilin F-actin depolymerization	Fei *et al.*,[57]
Glioma	The LN229 and U87MG human glioma cell lines *in vitro*	Anti-metastatic Inhibition of tumor proliferation ↓ Notch-1	Wang *et al.*,[58]
Osteosarcoma	U-2 OS cell *in vitro*	↑ Mitochondrial apoptosis pathway	Li *et al.*,[59]

transcription factor NF-κB. These findings suggest that zupatiline has a strong potential as a therapeutic drug for prostate cancer and further *in vivo* studies are needed to support its clinical application.[54] Eupatilin inhibited the expression of miR-21, which in turn mediated its effects on promoting apoptosis and inhibiting migration by targeting YAP1 in renal cancer cells. These findings suggested that Eupatilin might be an effective therapeutic agent for renal cell carcinoma.[55] Zhong *et al.* found that eupatilin inhibits and induces apoptosis in human RCC cells *via* ROS-mediated activation of the MAPK and PI3K/AKT signaling pathways. Consequently, eupatilin may serve as a potential

therapeutic agent for the treatment of human RCC.[56] Considering the detriments of drug toxicity and side effects in urinary system tumors, eupatilin, a natural flavonoid, demonstrates minimal toxicity, high safety, and efficacy, thereby presenting considerable clinical applicability. The anti-inflammatory and anti-oxidative stress properties of eupatilin complement its anti-tumor effects, showcasing distinctive advantages in urinary system tumor treatment. Further research and clarification of relevant mechanisms is warranted for clinical implementation.

THE ROLE OF EUPATILIN IN OTHER TUMORS

Eupatilin has shown promising aptitude for tumor prevention with diverse mechanisms of action, which brings hope to brain glioma patients. Fei *et al.* demonstrated that eupatilin significantly inhibits the viability and proliferation of glioma cells by arresting the cell cycle at the G1/S phase. Additionally, eupatilin disrupts the cytoskeleton structure and affects F-actin depolymerization through the P-LIMK/cofilin pathway, thereby inhibiting glioma migration. Eupatilin was also found to inhibit glioma invasion, potentially through the disruption of epithelial-mesenchymal transition and its impact on the RECK/matrix metalloproteinase pathway. However, no apoptosis-promoting effect of eupatilin on glioma cells was observed.[57] Moreover, Wang *et al.* reported that eupatilin has an anticancer effect on glioma cells, inhibits the proliferation, invasion and migration of glioma cells by inhibiting the Notch-1 signaling pathway, and promotes their apoptosis.[58] Li *et al.* found that eupatilin can trigger the mitochondrial apoptosis pathway, as manifested by enhanced Bax/B-cell lymphoma-2 ratio, decreased mitochondrial membrane potential, cytochrome c release, caspase-3 and-9 activation, and poly (ADP-ribose) polymerase cleavage detected in U-2OS cells. These results suggest that eupatilin can inhibit U-2OS cancer cell proliferation by inducing apoptosis through the mitochondrial intrinsic pathway. Therefore, eupatilin may represent a novel anticancer drug for the treatment of osteosarcoma.[59] In short, eupatilin exhibits extensive and robust antitumor properties, acting on multiple targets to hinder tumor proliferation, migration, and angiogenesis.

EFFECTS OF EUPATILIN ON OTHER DISEASES

Ciliopathy frequency involves disfunction of retinal photoreceptors. Small molecule drugs targeting ciliary defects in ciliopathy are currently lacking. CEP290, a gene implicated in various ciliopathies, encodes for a protein that forms a complex with NPHP5, critical for the ciliary transition zone. Kim *et al.* demonstrated that eupatilin enhanced ciliogenesis and improved ciliary receptor delivery. In rd16 mice with Cep290 mutations leading to blindness, eupatilin treatment enhanced opsin transport to photoreceptor outer segments and improved retinal light response. The rescue effect is due to eupatilin-mediated inhibition of calmodulin binding to NPHP5, thereby promoting the recruitment of NPHP5 to the ciliary base.[60] Furthermore, Wiegering *et al.* identified eupatilin as a potential therapeutic agent for ciliosis associated with RPGRIP1L mutations.[61] Eupatilin modulates retinal organoid gene expression, targeting ciliary and synaptic plasticity pathways in CEP290 mutants.[62] Additionally, eupatilin exhibited promise in addressing proliferative vitreoretinopathy. Cinar *et al.* found that eupatilin reduced the proliferation and transformation of TGF-β2-induced retinal pigment epithelial cells.[63] Du *et al.* demonstrated that eupatilin mitigates oxidative stress and apoptosis by activating the PI3K/Akt pathway in ARPE-19 cells, suggesting its potential for preventing or treating proliferative vitreoretinopathy.[64]

Eupatilin demonstrates therapeutic efficacy in various metabolic disease models, including diabetes, hyperlipidemia, and hypertension. Kang *et al.* observed that a 6-week eupatilin supplementation regimen significantly lowered fasting blood glucose levels, increased liver glycogen content, and enhanced both liver and plasma glucose metabolism, along with augmenting insulin secretion in type 2 diabetic mice.[65] Eupatilin exhibits the ability to mitigate hyperlipidemia by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, an enzyme targeted in hyperlipidemia therapy, as shown by Kim *et al.*[66] Furthermore, Kim *et al.* found that eupatilin significantly inhibited adipogenesis in 3T3-L1 adipocytes, reduced intracellular lipid accumulation in a concentration-dependent manner, and suppressed the expression of key adipogenic regulators, including PPARγ and CCAAT enhancer-binding protein α (C/EBPα). These findings suggest that eupatilin effectively inhibits 3T3-L1 cell differentiation and holds potential as a novel anti-obesity therapy.[67] Je *et al.* demonstrated that eupatilin modulates vasocontractile force, suggesting potential benefits in hypertension management. Interestingly, the mechanisms underlying the antihypertensive effects of eupatilin appear to involve endothelium-independent pathways, including the inhibition of Rho kinase and subsequent phosphorylation of MYPT1.[68]

SUMMARY OF THE PHARMACOLOGICAL POTENTIAL OF EUPATILIN

Eupatilin exhibits potent, broad-spectrum anti-inflammatory effects by regulating multiple signaling pathways, including JAK2/STAT3, TLR4/MyD88, PI3K/Akt, MAPK, and NF-κB, resulting in the inhibition of inflammation and the modulation of key inflammatory mediators.[17,20,22,70,71]

It has been shown to reduce inflammation and epithelial-mesenchymal transition in chronic rhinosinusitis, alleviate inflammation and coagulation in sepsis, improve lung injury, and protect against hepatocyte injury and hepatic steatosis.[16,65,70–72] These findings highlight versatility of eupatilin in managing inflammatory conditions and its potential as a therapeutic agent for various inflammation-related diseases.

The anti-tumor effects of eupatilin encompass cell cycle arrest, anti-proliferation, migration inhibition, angiogenesis suppression, and induction of tumor cell apoptosis. Furthermore, eupatilin demonstrates potential implications in cellular lipid metabolism, as indicated by studies investigating total lipid and fatty acid profiles.[73] Moreover, it exhibits additional anti-tumor properties, including the mitigation of cisplatin-induced nephrotoxicity, protection against cochlear hair cell apoptosis, and augmentation of 5-FU efficacy in colon cancer treatment. These attributes position eupatilin as a promising adjunctive agent in cancer therapy, warranting further elucidation of its underlying mechanism of action. Eupatilin exhibits potential chemoprophylactic properties and cytotoxic effects.[49,74–76]

Eupatilin shows potential as a treatment for various challenging conditions, including mitigating MPTP-induced symptoms of Parkinson's disease and dopaminergic neuron loss, addressing Cep290-related ciliopathies, reducing endometrial fibrosis, and inhibiting vocal cord fibrosis.[61,62,77–79] Its wide-reaching effects and low toxicity profile render it a promising therapeutic option for these rare and difficult-to-treat diseases.

LIMITATIONS OF EUPATILIN RELATED STUDIES

Studies on eupatilin predominantly focus on cellular and murine models, with *in vitro* investigations outnumbering *in vivo* experiments. Large-scale clinical trial data is limited, and there is insufficient repeated validation across multiple disease models. Further research is essential to establish its clinical efficacy and evaluate potential adverse effects.[43,54,66,69,80–82] There is no standardized dosage regimen for eupatilin across various diseases and animal models. Cytotoxicity testing indicated negligible cytotoxic effects of eupatilin within the concentration range of 1–500 μmol/L.[33] *In vitro* studies employed concentration gradients of 1, 25, 50, and 100 μmol/L for 1–2 h or 1–2–48 h of incubation.[17,23–25,38,52] Experimental dosages in mice or rats ranged from 1 mg/kg to 100 mg/kg, with treatment duration varying depending on the disease model. Generally, the middle to high dose range exhibited superior therapeutic efficacy, yet the optimal dosage for each condition remains undetermined.[18,39,72]

Eupatilin exhibits a diverse array of mechanisms, making it challenging to identify the influence of alternative pathways on specific pathological processes. For instance, besides NF-κB, eupatilin may also impact the MAPK and AP-1 pathways, which could stimulate the production of inflammatory mediators.[83] Eupatilin can concurrently activate MAPK and NF-κB signaling, yet the modulation of these two pathways and the possibility of cross-effects require further investigation.[34] Eupatilin potentially exerts its influence through multiple pathways, including PI3K/AKT, NF-κB, MAPK, and Nrf2, which may exhibit cross-influencing effects.[70] Therefore, it is imperative to exclude these cross-effects and intensify targeted studies on eupatilin.

PROSPECTS

Eupatilin is a highly regarded flavonoid that has the potential to fill the gaps in existing drug treatments due to its diverse and far-reaching health benefits. Its multi-target approach to inflammation stands out, engaging with complex biological pathways and regulating a variety of cellular and molecular targets, which sets it apart from conventional anti-inflammatory drugs. With a strong track record in reducing both acute and chronic inflammation across various body systems, eupatilin not only mitigates inflammation but also aids in the reversal of inflammatory processes, enhancing recovery and improving outcomes.[17,19,22,39,71]

The safety of eupatilin, evidenced by its minimal impact on physiological balance and its low side-effect profile, underscores its potential for broad clinical use.[21,25] In oncology, anti-tumor capabilities of eupatilin are remarkable, effectively targeting a spectrum of cancers through diverse mechanisms that include inhibiting cell proliferation and promoting apoptosis. Its synergistic effect with chemotherapy drugs like cisplatin, by reducing their toxicity while enhancing the destruction of tumor tissue, highlights its potential to improve cancer treatment strategies.[74,75]

In addition, the ability of eupatilin induce tumor cell differentiation makes it a promising complementary anticancer therapy.[43] Its potential extends to treating rare and chronic conditions, suggesting that further research could unlock new clinical applications. The future of eupatilin looks bright, with its capacity to address unmet needs in medicine and contribute to the advancement of patient care.

Notably, current research on eupatilin primarily employs intravenous or intraperitoneal administration routes, both of which are systemic delivery methods. However, these

systemic approaches may not achieve optimal dose-effect ratios for certain non-systemic diseases or localized manifestations of systemic diseases.[84,85] Consequently, there is a compelling rationale for developing or employing existing localized drug delivery systems to improve the administration of eupatilin. This strategy could be pivotal in expanding the therapeutic indications of eupatilin and enhancing its clinical efficacy. The potential of eupatilin can be significantly expanded through the incorporation of novel drug delivery systems, such as nanovesicles, hydrogels, and inflammation-responsive biomaterials.[86–89] These advanced carriers play a crucial role in enhancing the targeted release of eupatilin at specific sites, increasing the effective drug concentration, and reducing systemic side effects. For instance, nanovesicles can encapsulate eupatilin, protecting it from degradation and facilitating its controlled release directly at the site of inflammation.[86,87] Hydrogels, with their unique ability to retain large amounts of water, can provide a sustained release of eupatilin, maintaining therapeutic levels over extended periods.[88] Furthermore, inflammation-responsive biomaterials can be engineered to release eupatilin in response to inflammatory stimuli, ensuring that the drug is delivered precisely when and where it is needed most.[89,90] This precision not only maximizes the therapeutic impact of eupatilin but also minimizes the risk of adverse reactions, thus enhancing its safety profile. By leveraging these innovative drug delivery technologies, the therapeutic applications of eupatilin could be broadened to include a wider range of inflammatory and tumor conditions, offering new hope for patients with complex and refractory diseases. As research progresses, these advanced delivery systems could pave the way for more effective and safer clinical applications of eupatilin, making it a versatile and valuable addition to modern pharmacotherapy.

CONCLUSIONS

Eupatilin, a flavonoid with diverse therapeutic potential, has been the subject of increasing research, particularly for its anti-inflammatory, anti-tumor, and cytoprotective properties. It offers a unique approach, differing from traditional single-target anti-inflammatory and anti-tumor drugs by engaging multiple pathways and regulating various targets. Eupatilin shows significant inhibitory effects on inflammation in multiple organ systems and has the potential to reverse the inflammatory process, improving recovery and prognosis. With a commendable safety profile and minimal side effects, it holds promise for the treatment of various tumors and rare diseases. However, challenges remain in terms of understanding its side effects, determining the therapeutic dose, and validating its efficacy *in vivo*. Despite these challenges, high safety profile and notable pharmacological effects of eupatilin suggest it has the potential to benefit a broader population in the future with further research.

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Author Contributions

ZL, XW, KT, DH, JS conceived the article and wrote the manuscript. KT, DH, JS conducted language editing. QZ, WM and YH designed and oversighted the work, revised and approved the final version. All authors contributed to the article and approved the submitted version.

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Ethical Approval

No applicable.

Informed Consent

Not applicable.

Conflict of interest

All authors declare that there are no competing interests.

Use of Large Language Models, AI and Machine Learning Tools

None declared.

Data Availability Statement

No additional data is available.

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