Evodiamine and Its Role in Chronic Diseases

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Abstract Evodiamine (EVO) is a major alkaloid compound extracted from the dry unripened fruit Evodiae fructus (*Evodia rutaecarpa* Benth., Rutaceae). EVO has a variety of pharmacological activities, such as anti-obesity, anti-allergenic, analgesic, anti-tumor, anti-ulcerogenic, and neuroprotective activities. EVO has varying efficacies in animal models and humans. Here, the physicochemical properties of EVO are presented, and the EVO's functions and mechanisms of action in various chronic diseases are reviewed. EVO is worth exploring in more depth in the future for its potential use in various chronic diseases.

Keywords Evodiamine · Physico-chemical properties · Cell signaling pathways · Pharmacologicalactivities · Mechanisms of action · Chronic diseases

1 Introduction

Evodiamine (EVO) is the main bioactive component extracted from the dry unripened fruit of Evodiae fructus (Chinese name is Wu-Chu-Yu) or other Tetradium genus of plants. EVO has a variety of pharmacological activities, such as anti-obesity, anti-inflammatory, and anti-tumor. The role of EVO in various chronic diseases and its possible mechanisms of action are outlined here.

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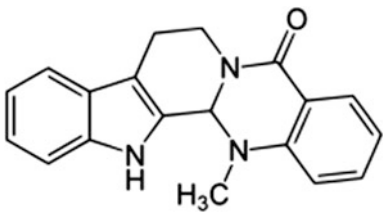

Fig. 1 Structure of evodiamine

2 Physicochemical Properties of Evodiamine

EVO (CAS: 518-17-2) is a plant alkaloid and its systematic name is 21-methyl-3,13,21-triazapentacyclo[11.8.0.02,10.04,9.015,20] henicosa-2(10),4,6,8,15,17,19-heptaen-14-one (Fig. 1). EVO is a pale yellow crystal with no perceptible odor or taste. The main physicochemical parameters of EVO are listed in Table 1. EVO can be assayed using an ultraviolet spectrophotometer at 225 nm or by a high-performance liquid chromatography system using an internal standard method [1].

3 Modulation of Cell Signaling Pathways by Evodiamine

3.1 Anti-obese Action

EVO induces the phosphorylation of EGFR, PKCα, and ERK, and it inhibits adipogenesis via the EGFR–PKCα–ERK signaling pathway [2]. EVO inhibits adipocyte differentiation in 3T3-L1 and C3H10T1/2 cells [3]. The anti-obese mechanism of action of EVO is reported to be similar to that of capsaicin [4].

3.2 Anti-inflammatory and Anti-allergenic Action

EVO exerts an anti-inflammation activity on human umbilical vein endothelial cells (HUVEC) with high glucose by suppressing the P2X4 receptor (P2X4R) signaling pathway, accompanied by the downregulation of NF-κB, TNFR-α, P2X4R, and intracellular reactive oxygen species (ROS), and upregulation of the nitric oxide

Table 1 The main physicochemical parameters of evodiamine

Molecular formula	Molecular weight	Appearance	Solubility	Melting point	Boiling point	Density	Refractive index	Storage temperature
C19H17N3O	303.36	Fine powder	Insoluble	263–265 °C	575.1 °C	1.39 g/cm^3	1.764	2–8 °C

(NO) level [5]. EVO inhibits the secretion of interleukin (IL)-10 and decreases production of IL-2 from the LPS-stimulated endothelial cells [6]. EVO inhibits LIGHT-induced migration via the suppression of ROS production and NADPH oxidase activation in human monocytes [7]. EVO represses hypoxia-induced COX-2 expression by inhibiting hypoxia-inducible factor 1-alpha which is mediated by the dephosphorylation of Akt and p70S6K in RAW264.7 cells [8]. EVO exerts an anti-allergenic effect by inhibiting the protein levels of TNF-α and IL-4 induced by the IgE–antigen complex in RBL-2H3 cells [9].

3.3 Analgesic Effect

EVO induces significant increases in intracellular calcium and inward currents in dorsal root ganglion neurons and the transient receptor potential (TRP) V1-transfected HEK293 cells, which suggests that EVO suppresses thermal hyperalgesia by activating TRPV1 channels [10].

3.4 Mechanistic Aspects of Evodiamine in Cancer Cells

EVO has a high binding affinity and selectivity to potential vanilloid-1 (TRPV1). It may be used for the treatment of cancer cells by acting as a TRPV1 agonist [11] or aryl hydrocarbon receptor (AhR) antagonist [12].

3.4.1 Respiratory System Tumor Cells

Lung Cancer Cells

EVO inhibits the A549 cell proliferation via metadherin suppression and apoptosis activation [13]. EVO induces arrest at G2/M phase and apoptosis via the mitochondrial and endoplasmic reticulum pathways in H446 and H1688 cells [14].

Nasopharyngeal Carcinoma Cells

EVO inhibits the invasion and metastasis of NPC cells via repressing the expression and activity of MMP2 and attenuating the phosphorylation level of ERK1/2 [15].

3.4.2 Circulating Tumor Cells

Leukemia Cells and Resistant Leukemia Cells

EVO inhibits the K562 cell proliferation by regulating the peroxisome proliferator-activated receptor-gamma (PPARγ) pathway via downregulating cell cycle control protein cyclin D1 and upregulating cyclin-dependent kinase inhibitor p21 [16].

Resistant Leukemia Cells

EVO exhibits increased inhibition against camptothecin-resistant K562, THP-1, CCRF-CEM, and CCRF-CEM/C1 cells by acting as a dual catalytic inhibitor of topoisomerases I and II [17].

3.4.3 Digestive System Tumor Cells

Gastric Cancer Cells and Cancer Stem Cells

EVO inhibited proliferation and induced apoptosis in SGC7901 cells via suppressing survivin and increasing caspase-3 mRNA [18]. EVO inhibits proliferation and sphere formation ability of gastric cancer stem cells (GCSCs) via repressing the Wingless and INT-1 (Wnt)/β-catenin signaling pathway and represses the induced pluripotent stem cell factors and epithelial-to-mesenchymal transition (EMT) factors [19].

Oral Cancer Cells

EVO inhibits MC3 and HSC4 cell proliferation and induces apoptosis by reducing phosphorylated AKT expression [20].

Colorectal Cancer Cells

EVO exerts anti-proliferative effects by downregulating IGF-1/HIF-1α expression in LoVo cells [21]. In HCT-116 cells, EVO inhibits proliferation, induces S and G2/M arrest, induces apoptosis via the p53 signaling pathway, and inhibits migration by downregulating the expression of matrix metalloproteinase 3 (MMP3) by inactivating the JAK2/STAT3 pathway [22]. In HCT-116/L-OHP cells, EVO inhibited growth and induced apoptosis in a dose- and time-dependent manner, reduced the accumulation of rhodamine 123 and the activity of ATPase, and inhibited phosphorylation of the NF-κB pathway, such as p50/p65. Thus, EVO may suppress ABCG2-mediated drug resistance (MDR) by inhibiting the p50/NF-κB pathway [23].

Pancreatic Cancer Cells

EVO increases the anti-pancreatic cancer effect of gemcitabine in SW1990 cells via downregulating PI3K/Akt pathway [24].

Hepatocellular Carcinoma Cells

EVO inhibits STAT3 tyrosine 705 signaling by inducing phosphatase shatterproof 1 in HepG2 cells [25].

3.4.4 Urologic Cancer Cells

Renal Proximal Tubular Epithelial Cells

EVO inhibited transforming growth factor (TGF)-β1-induced epithelial–mesenchymal transition (EMT) in rat NRK52E cells. Smad-2 and the PPARγ signal pathway participated in promoting the effects of evodiamine [26].

Bladder Cancer Cells

EVO enhances tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in 253J and T24 cells through an mTOR/S6K1-mediated reduction of Mcl-1 levels [27].

3.4.5 Genital Carcinoma Cells

Breast Cancer Cells and Resistant Breast Cancer Cells

As a topoisomerase-1 inhibitor, EVO facilitates the formation of topoisomerase I-DNA cleavable complex in MCF-7 breast cancer cells [28]. EVO induces apoptosis of doxorubicin (DOX)-sensitive MCF-7 and DOX-resistant MCF-7/ADR cells by increasing cleaved poly(ADP-ribose) polymerase (PARP), caspase-7/9, and caspase activities, as well as inhibiting the Ras/MEK/ERK cascade and inhibitors of apoptosis (IAPs) [29].

Ovarian Cancer Cells

EVO has anti-proliferative effects on ovarian epithelial cancer cells, A2780 and A2780/PTX(R), induces G2/M arrest mediated by cyclin B1 and Cdc2, and, via the

MAPK signaling pathway, improves chemo-resistance by downregulating MDR-1 expression [30].

3.4.6 Brain Tumor Cells

Glioblastoma Cells

EVO stimulates U87 cells to tumor necrosis factor-α-related apoptosis-inducing ligand (TRAIL) via the death receptor pathway by increasing the death receptor (DR) 4, DR5, caspase-8, and cleaved caspase-3 [31].

Neuronal Cells

When tested against the S, XS [11], L(G), L(A), XL [17], and XL [18] alleles, 2 μM EVO increased 5-HTT promoter (the serotonin transporter) activities by 220, 80, 310, 180, 175, and 102 %, respectively. EVO increased promoter activity depending on the genetic variation of the 5-HTTLPR polymorphism [32].

3.4.7 Osteosarcoma Cells

EVO inhibits OS 143B cell proliferation by upregulating phosphatase and tensin homolog (PTEN) levels through blocking PI3K/Akt signaling [33].

3.5 Antibacterial Effect

Through inhibiting topoisomerase I and supercoiled plasmid DNA relaxation, EVO has a significantly lower minimal inhibitory concentration (MIC) compared with five antibiotics including cefotaxime and aztreonam (128 vs. >512 μg/mL) against the clinical isolate of *Klebsiella pneumoniae* [34].

3.6 Anti-virus Effect

EVO acts against influenza A virus (IAV) by markedly inhibiting IAV replication and IAV-induced autophagy via the AMPK/TSC2/mTOR signal pathway, blocking LC3-II, p62 and EGFP-LC3 aggregation; retarding Atg5–Atg12/Atg16 heterotrimer formation; decreasing Atg5, Atg7, and Atg12 expressions; and blocking TNF-α, IL-1β, IL-6, and IL-8 cytokine release [35].

3.7 *Effects on Cerebral or Cardiac Ischemia*

EVO induces transient receptor potential vanilloid-1 (TRPV1) and calcium-mediated protective autophagy through a calcium/c-Jun N-terminal kinase (JNK) pathway in U87-MG astrocytes [36]. EVO inhibits β1-AR activity by downregulating cAMP and PKA in Chinese hamster ovary cells with high expression levels of β1-AR (β1-AR/CHO-S cells) [37]. EVO may prevent cardiac ischemia–reperfusion injury via energy modulation [37].

3.8 *Insulin-Sensitizing Effect or Insulin Resistance*

EVO activates AMP-activated protein kinase (AMPK) via the Ca(2+)-dependent PI3K/Akt/CaMKII signaling pathway and promotes the high molecular weight adiponectin multimerization in 3T3-L1 adipocytes [38].

4 Role of Evodiamine in Chronic Diseases

EVO is an indole alkaloid extracted from the traditional Chinese medicinal herb *Evodia rutaecarpa* (Rutaceae family). EVO and *E. rutaecarpa* are currently used for the treatment of headaches, abdominal pain, vomiting, colds, and reduced blood circulation in the clinic practices of doctors of traditional Chinese medicine in some southeast countries such as China, Japan, and Korea.

Chronic disease is defined by the World Health Organization as a generally slow-progressing disease of long duration. EVO plays positive roles in curing some chronic diseases, such as cancer, diabetes, and cardiovascular diseases [39], by intervening on the risk factors and underlying determinants linked with chronic diseases. EVO may be a potential therapeutic drug against other chronic diseases such as renal tubulointerstitial fibrosis [26], atherogenesis [7], hypoxia [8], glioma [31], hypomotility disorders [40], and IgE-induced allergenic diseases, including atopic dermatitis and rhinitis [9]. EVO may prevent cardiac ischemia–reperfusion injury via energy modulation [37].

5 Biological Activities of Evodiamine in Animal Models

EVO possesses a variety of biological activities, such as anti-obesity, anti-inflammatory, anti-nociceptive, anti-cancer, antibacterial, and antidepressant-like effects. The biological effects of EVO are tested in various animal models.

5.1 Anti-obese Effect

EVO suppresses neuropeptide Y (NPY) and agouti gene-related protein (AgRP) mRNA level in the hypothalamus and decreases the food intake in male rats [41]. EVO acts as a nonpungent vanilloid receptor agonist. When the mice were fed evodiamine as 0.03 % of their diet for 12 days or the rats were given with evodiamine-containing ethanol extract of Evodia fruits at 0.02 % for 21 days, the body weights, perirenal and epididymal fat weights, the levels of free fatty acid in sera, and total lipids, triglyceride and cholesterol in the liver decreased markedly compared with the control group [4]. EVO influences lipid metabolism by decreasing the expression of lipogenesis genes, such as the expression of peroxisome proliferator-activated receptor-g (PPARg), sterol-regulatory element binding protein (SREBP-1c), and fatty acid synthase, as well as increasing the expression of lipolysis genes, such as the expression of hormone-sensitive lipase. In addition, EVO reduces body weight and heat [42]. EVO reduces body weight gain and the blood glucose levels in db/db mice [3].

5.2 Anti-allergic Effect

EVO has anti-allergic effects and inhibits passive cutaneous anaphylaxis (PCA) reaction and scratching behaviors in ICR mice [9].

5.3 Analgesic Effect

EVO pretreatment decreased thermal hyperalgesia induced by intraplantar injection of capsaicin in adult rats [10]. The analgesic effect of EVO may be due to the desensitization of TRPV1 in sensory neurons [10].

5.4 Anti-tumor Effects

EVO (20 mg/kg/day) significantly inhibited xenograft HepG2 tumor growth in nude mice by blocking STAT3 signaling after 13 days being orally administered [25].

5.5 Anti-ulcerogenic Activity

Pretreatment of EVO markedly suppressed the Rho, Rho-kinase 1 and 2, and cytosolic and nucleic necrosis factor (NF)-κBp65 expression against

ethanol-induced gastric ulcer in mice [43]. Evodiamine pretreatment obviously increased the glutathione, superoxide dismutase, and catalase levels in sera and lowered the malonaldehyde level and myeloperoxidase activity in the stomachs of mice [43].

5.6 Neuroprotective Effect

EVO protects the brain from cerebral ischemic damage in mice through upregulating pAkt, pGSK3β, and claudin-5, downregulating NF-κB expression, and ameliorating blood–brain barrier permeability [44].

5.7 Antidepressant-Like Effect

EVO can reverse the chronic unpredictable mild stress-induced behavioral deficits and biochemical changes in chronic unpredictable mildly stressed rats. The mechanisms are related to the modulation of the monoamine transmitters and brain-derived neurotropic factor tropomyosin-related kinase B [45].

5.8 Alzheimer's Disease

EVO improves the learning ability and memory in transgenic mice with Alzheimer's disease by reversing the glucose uptake inhibition and decreasing IL-1β, IL-6, TNF-α, and COX-2 expression [46].

5.9 Prevention of Insulin Resistance

EVO reduces the insulin-stimulated mammalian target of rapamycin and ribosomal S6 protein kinase (mTOR-S6K) signaling and insulin receptor substrate 1 (IRS1) serine phosphorylation in white adipose tissues and improves glucose tolerance in obese/diabetic KK-Ay mice [47].

5.10 Cardiotonic Effect or Remedy for Cardiac Diseases

EVO evokes transient positive inotropic and chronotropic effects on the atria of the guinea pig, which is due to its interaction with the vanilloid receptors and the

release of the calcitonin gene-related peptide antagonist (CGRP) [4]. EVO attenuates myocardial infarct size, improves metabolism disorders between fatty acids and glucose, increases ATP and Ca(2+)-ATPase activity, and reduces the peroxisome proliferator-activated receptor-α (PPARα) protein level in the myocardial ischemia–reperfusion (I/R) rats [37].

5.11 Other Effects

EVO exerts stimulatory effects on rat jejunal contractility, exhibiting its potential role in relieving hypomotility disorders [40]. EVO improves the undesirable effects of some drugs while preserving their pharmacological activities. For example, the side effects (adipogenesis, body weight gain, and hepatotoxicity) of rosiglitazone can be attenuated by being co-administered with EVO, but the blood glucose-lowering effect of rosiglitazone is still well preserved [3].

6 Biological Activities of Evodiamine in Humans

There are few reports of the biological activities of EVO in humans. Evodiae fructus is reported to be used as an analgesic in traditional Chinese medicine [10]. The typical commercial preparation of traditional Chinese medicines containing EVO is the Zuojin pill. The Zuojin pill is composed of Evodiae fructus and Rhizoma (the mass ratio is 1:6). The Zuojin pill inhibits gastric emptying and the secretion of gastric acid. The Zuojin pill also has an obvious anti-ulcer effect [48]. The Zuojin pill is officially listed in the Chinese Pharmacopoeia.

7 Conclusions

EVO is a major bioactive alkaloid isolated and purified from the Chinese herbal drug “Wu-Chu-Yu” (Evodiae fructus). It possesses a multitude of positive effects, such as anti-cancer and anti-nociceptive effects on different cells, including stem cells, animals, and humans through modulating diverse targeting regions or through various signaling pathways. Evodiae fructus or the extraction of Evodiae fructus, such as ethanol, methanol, and chloroform extracts, exhibits some effects similar to those of EVO [49]. EVO can be used alone or in combination with other drugs. The combination therapy of EVO with gemcitabine augments its therapeutic effects [24]. Furthermore, EVO shows little toxicity against normal cells [50] in contrast to its positive effects.

In the future, three measures are recommended to be pursued in order to promote the clinical application of EVO in the treatment of chronic diseases: First is to

develop a new EVO delivery system, such as a supermolecular nanoemulsion [51] or a phospholipid complex [1], in order to modify the pharmacokinetic behavior and increase the bioavailability of EVO; second is to chirally separate two EVO stereoisomers because sometimes the S-(+) EVO is more effective than the R-(−) evodiamine [52]; third is to synthesize new derivatives with much better potency and less toxicity [53], such as carbamates [54], compared with the parent drug EVO.

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