LUPINE PUBLISHERS
Open Access

Open Access Journal of Oncology and Medicine

DOI: 10.32474/OAJOM.2018.01.000111

ISSN: 2638-5945

Review Article

Re-Purposing Evodiamine as an Anti-Cancer Drug: Effects on Migration and Apoptosis

Tomas Koltai*

Independent researcher, Italy

Received: March 27, 2018; **Published:** April 05, 2018

***Corresponding author:** Tomas Koltai, Independent researcher, Florence, Italy

Abstract

Introduction: Evodiamine is a quinolone alkaloid compound obtained from a fruit described in traditional Chinese medicine. It has been in use for many centuries for the treatment of headaches, menstrual problems, abdominal pain and other ailments. In the western world, it is known as a controversial weight loss product and is sold over the counter as a nutritional supplement. Many freely sold weight loss products contain evodiamine associated with other supposed weight control chemicals. Even though there are no reliable statistics, we may presume that thousands of persons have been using it without serious side effects being reported.

Background: At the beginning of this century researchers found that this compound had anti-cancer effects: cytotoxicity and decreased invasion and migration in vitro in malignant cells while showing minimal damage to normal cells. Little has been investigated about in vivo effects on cancer. There is a lack of information regarding the possibility of achieving the clinical concentrations needed for tumour cytotoxicity and for inhibiting migration.

Objectives: The goal of this study was to determine the feasibility of re-purposing evodiamine as an anti-cancer drug. For this, we investigated:

a. the possibility of achieving the cytotoxic concentrations of the drug required at tumor level in the clinical setting;

b. the molecular mechanisms responsible for the anti-cancer effects;

c. which types of tumours can be treated;

d. its interrelation with other chemotherapeutics;

e. Interrelation of evodiamine with berberine in anti-cancer effects.

Material and Methods: Due to the abundance of published research on evodiamine, many of the objectives could be accomplished by reviewing the literature, introducing a systematic search, and organizing the findings.

Results: The necessary concentrations to achieve possible clinical results may be reached through oral administration. This concept applies mainly to inhibition of migration, that requires a low concentration. The cytotoxic effects need higher concentrations that are not easily attainable with standard preparations. An association with berberine, a non-toxic compound, increases evodiamine's cytotoxicity. Almost all malignancies, whether solid or hematologic, are affected by evodiamine in a dose dependent manner. Evodiamine may also complement the activity of other chemotherapeutics like campthotecin, taxanes, doxoubicin and probably radiotherapy as well.

Conclusion: Evodiamine should be tested in humans to establish the achievable plasma concentrations, because all the published pharmacodynamic reports were based on tests on rodents. Whether alone or associated with berberine, evodiamine,deserves to be tested in well designed clinical trials for the treatment of cancer and prevention of metastasis.

Keywords: Evodiamine; Cancer; Apoptosis; Migration; Metastasis; Berberine

Introduction

The search for pharmacologically interesting drugs among traditional Chinese herbs has been the origin of a few important success stories. That is the case, for example, of artemisinin and its derivatives in the treatment of malaria. This drug has proven to be the most important innovation in malaria treatment in the last fifty years. However, there are other interesting molecules among Chinese herbs that did not achieve the same success and in a certain way; they have been neglected in terms of research and development. Evodiamine (EVO) is one of those drugs. EVO is a natural compound, a quinolone alkaloid isolated from the fruit of Evodia rutaecarpa (Wu-Chu-Yu is the Chinese name). In China, the dried unripe fruits of Evodia rutaecarpa have been traditionally used for the treatment of a variety of symptoms like abdominal pain, headache, menstrual disturbances and postpartum haemorrhage [1]. In the west, EVO obtained from this fruit has been used as a weight loss dietary supplement (under the brand name of Evodia and others), in spite of the fact that its weight loss properties have never been scientifically demonstrated and are still controversial.

Table 1: Pharmacological activities of EVO other than anti-cancer effects.

Action	Reference
Stimulation of cathecolamine secretion	[2]
Pain relief	[3]
Anti-inflammatory	[4,5]
Weight loss through increased thermogenesis (weight loss with EVO is a controversial issue which has not been fully clarified)	[6-8]
Vasodilation	[9]
Inhibitory effects on the synthesis of prostaglandin E2 (PGE2), this can be considered as part of its anti-inflamatory effects.	[10]
Increased insulin sensitivity	[11]
Increase secretion of testosterone by the testicle	[12]
Ureterotonic effect	[13]
Diuretic effect through the inhibition of aldosterone release	[14]
Protection of myocardial muscle in the ischemia-reperfusion process	[15]

In the last fifteen years there has been growing evidence that EVO exerts anti-cancer activity. EVO has different pharmacological actions that are summarized in Table 1 (which shows the wide spectrum of diverse effects of this compound), but we are only considering in depth those related to anti-cancer effects. The important fact is that it has been tested in humans as a dietary supplement and no important adverse effects were found [2], however, it was mixed with other weight loss products and dose has not been clearly established. In other human experiments of the same kind, it was used at a dose of 500 mg in one intake [3]. An ANSES (French Agency for Food, Environmental and Occupational Health & Safety) publication [4] analyzing the risks and adverse events of food supplements stated that: "The adverse effects of evodiamine may be related to its ability to activate the capsaicin receptor underlying its positive inotropic and chronotropic actions [5,6] and vasodilator actions (risk of hypotension) (Kobayashi et al. 2000)".

Another paragraph on the issue ANSES says: "The major alkaloids of Evodia, evodiamine and rutaecarpine, have modulatory effects on metabolizing enzymes, in particular cytochromes P450 CYP3A4, CYP1A2 and CYP1A1 (Ueng et al. 2002; Wen et al. 2014) [7] which metabolize many drugs". No other major adverse effects are described in this "opinion" of ANSES, and no other warnings are given. At this point, we may assume that the main adverse effects and tolerable doses are known. Furthermore, it is an over the counter drug that is probably widely used for its (real or fake) weight loss effect.

EVO`s effects related to anti-cancer activity

EVO has shown inhibitory effects on migration of MDA-MB-231 breast cancer cells with a significant reduction of lung metastasis. It also induced cancer cell apoptosis through caspase activation. EVO-treated xenografted mice with MDA-MB-231 showed a reduction of nearly 50% in lung metastasis when compared with the control group [8,9]. EVO also exhibited an important cytotoxic activity against other tumors like colon and hepatoma human cell lines [10,11]. Table 2 shows different malignant cell lines where EVO has anti-cancer effects. In spite of the evidence of a cytotoxic activity of EVO on different lines of cancer cells, EVO did not show toxicity against normal cells [12].

Table 2.

Tumour	References
Breast	[19-26]
Colorectal	[27,28]
Gastric	[29-33]
Liver	[34,35]
Pancreas	[36]
Thyroid	[37]
Non small-cell lung cancer	[38,39]
Small-cell lung cancer	[40]
Prostate	[41-43]
Bladder	[44]
Leukemia	[45]

Melanoma	[46]
Nasopharyngeal carcinoma	[47]
Renal carcinoma cells	[48,49]
Urothelial cell carcinoma	[50]
Glioblastoma	[51]
Ovarian	[52-54]
Osteosarcoma	[55,56]
Oral cancer cells	[57]
Cervical cancer (HeLa)	[58]

EVO`s mechanisms of action on malignant cells

The evidence outlined above clearly shows that EVO acts as a cytotoxic agent for malignant cells without affecting the normal cells (or affecting them minimally). It is necessary now to describe the mechanisms involved in the anti-cancer activity.

Apoptosis

The experimental research shows that EVO is an apoptotic inducer of malignant cells. In the case of HeLa cervical cancer the mechanism described is caspase dependent because it can be eliminated with caspase inhibitors. The caspase dependent apoptosis in HeLa also showed increased expression of Bax and decreased expression of Bcl-2 which means an alteration of the Bax-Bcl-2 balance [13]. Lee et al [14] found that EVO could develop its pro-apoptotic activity through caspase dependent and caspase independent mechanisms in leukemic cells. Whether EVO's apoptotic mechanisms are cell- or tissue-dependent has not been clarified but on Table 3 we can see that apoptosis induced by EVO has been found in all the malignant cell lines tested. Table 3 lists the cells where apoptosis is one of the mechanisms of EVO's anti-cancer effects.

Table 3.

Apoptosis has been described in:	References
Leukemic U937 cells.	[45]
Leukaemia K562 cell line	[62,63]
Leukemic T-lymphocytes	[73]
Human myeloid leukaemia KBM5	[74]
Cervical cancer HeLa cells	[58,69]
Breast cancer cells: MCF-7	[19]
MCF-7 doxorubicin resistant	[25]
NCI/ADR-RES cells	[23]
Renal carcinoma cells: Caki-1	[49]
Hepatocellular carcinoma Hepa 1-6; HepG2 cell lines.	[59,60,64]
Bel-7402 hepatoma cell line	[65]
SMMC-7721 hepatoma line	[35]
Urothelial cell carcinoma	[50]
Glioblastoma: U87 and C6 cells	[51]
Human lung cancer A549 and H1299 cells.	[61,38,74]
Human ovarian cancer cells HO-8910PM and	[52]
A2780, A2780CP, ES2, SKOV-3	[53]
Gastric carcinoma stem cells	[30]
Colorectal cancer cell HCT-116	[65]
COLO205 and HT-29	[27]
Gastric carcinoma cells SGC-7901	[66,67]
Osteosarcoma	[56]
Human small-cell lung cancer H446 and H1688	[40]
Melanoma A375-S2 cells	[70-72]
Prostate DU145 and PC3	[41,43]
LnCaP	[42]
Human squamous cell carcinoma FaDu	[74]
Jurkat human T-cell lymphoma	[74]
Human multiple myeloma U266	[74]
Murine fibrosarcoma L929	[77]
No effects on normal human peripheral mononuclear blood cells.	[77]

This apoptosis seems to be p53 independent and may involve both, extrinsic and intrinsic apoptotic pathways [15]. It has also apoptotic effects on cancer stem cells [16]. The mechanism of cell death is not only apoptotic, it may also be necrotic [17]. The first cytotoxic finding is apoptosis, but 15 micromol/L of EVO induced necrosis after 24 hours of incubation. As mentioned, the apoptosis may be reached by caspase dependent and caspase independent pathways, but also through Fas-L/NF-kB (76), PI3K/Akt/caspase [18], and the sphingomyelin pathway [19]. SIRT1 and protein kinase C inhibition may also represent another apoptotic pathway [20].

Inhibition of migration, invasion and metastasis

Migration is the first step of invasion and eventual metastasis. EVO has shown clear signs of its ability to inhibit migration and therefore reduce the number of metastases. The evidence is summarized in Table 4. Ogasawara et al. [9] attributed the anti-migratory effects of EVO to the methyl group at N-14 and the hydrogen at C-13b. It is important to underline that migration inhibition can be achieved with low concentrations of EVO that are perfectly obtainable in the clinical setting as we shall see below. The molecular mechanism that EVO employs for inhibiting migration, even if not fully known, may be centered on the protein cortactin, considered by Maders et al. as the "master switch" of the invadopodia [21]. When cortactin is phosphorylated it polymerizes the actin fibers in the invadopodia and at the same time intervenes in extracellular matrix proteolysis by modulating metalloproteases release. These steps are a pre-requisite for migration. Even if the full process is not fully known (Figure 1 & 2).

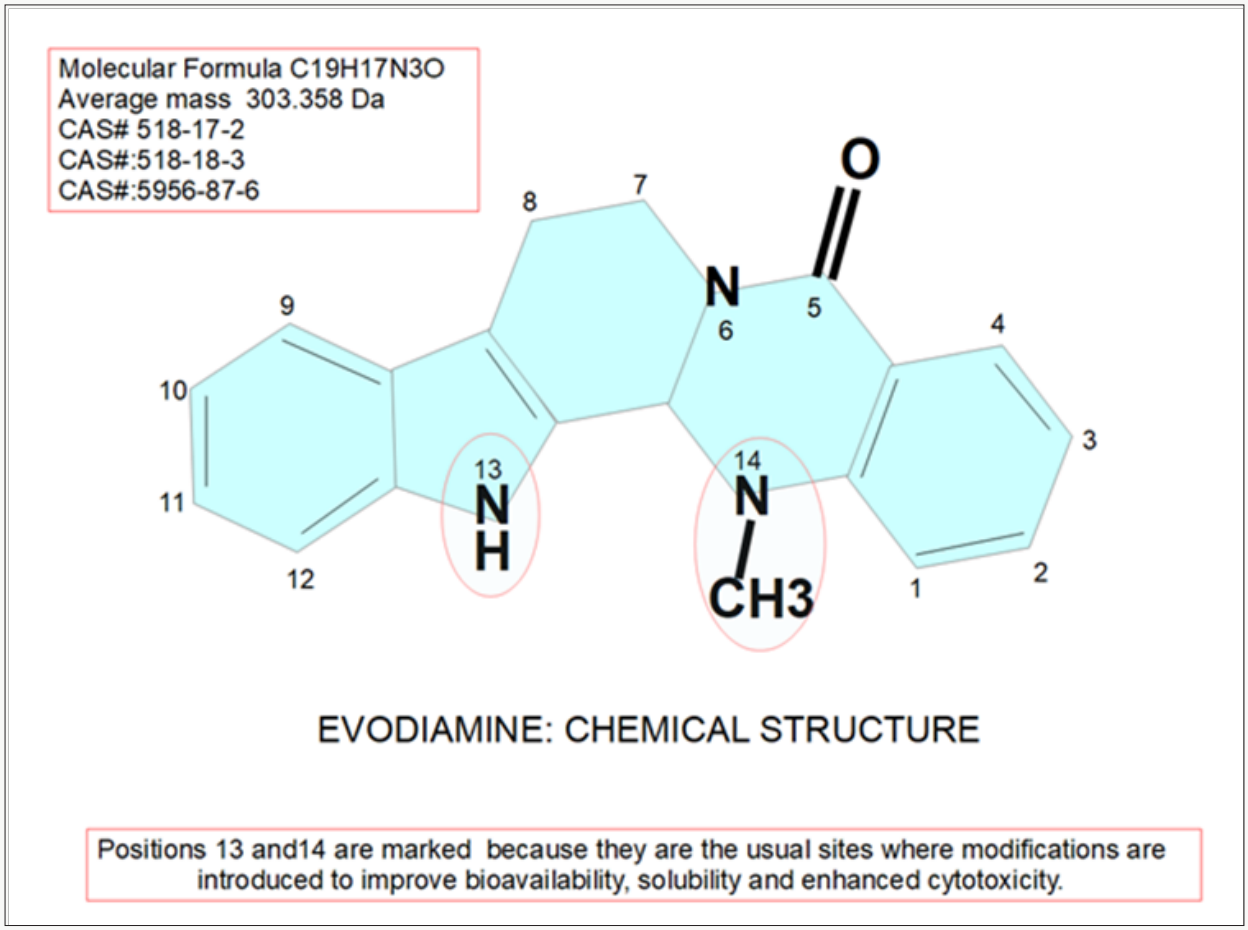

Figure 1: Evodiamine chemical structure. Derivatives with improved anti-cancer capacities or increased solubility, usually introduce modifications in positions 13 and 14. EVO was the first alkaloid isolated from E. rutaecarpa's fruit and is the main active principle of this plant.

Table 4.

Reference	Findings
[19]	EVO reduced metastasis in MDA-MB-231 breast cancer cells.
[20]	EVO showed anti-invasive and anti-metastatic effects on Lewis lung carcinoma, B16-F10 melanoma and colon 26-L5 carcinoma. The experiments with 26-L5 tumor cell inoculation after incubation with EVO significantly decreased the number of liver and lung metastasis.
[21]	After examining 75 natural compounds, searching their inhibitory effect on migration and proliferation of colon cancer cells, EVO was found to be the most potent and selective inhibitor of tumor cell migration. This inhibition was achieved with concentrations 20 times lower than the one needed to inhibit tumor proliferation.
[47]	EVO inhibited the migration of HOME1 and CNE1 nasopharyngeal cancer cells without affecting proliferation; it decreased MMP2 expression and activity without affecting MMP9, and inhibited the translocation of NF-kB p65. The authors attributed these actions to the attenuation of ERK1/2 phosphorylation.
[48]	EVO modifies the expression of many genes related to migration in renal cell carcinoma.
[65]	EVO inactivated the JAK2/STAT3 pathway which lead to decrease in MMP3`s expression in HCT-116 human colorectal cells and decreased migration.
[74]	The authors propose the EVO modulation of NF-kB as the main mechanism for decreasing proliferation, invasion and metastatic behavior.
[79]	When HUVEC is stimulated with TGF-β1 there is increased migration. EVO blocked this increase. EVO also blocked the activation of Smad2, Smad3, ERK1/2, and Akt, and nuclear translocation of Smad4 in HUVEC.
[80]	EVO decreased expression of metalloproteinases and cell adhesion molecules through activation of the expression of peroxisome proliferator-activated receptor γ (PPARγ) and its translocation to the nucleus.
[81]	The antimigratory properties of Evo in LIGHT induced migration of monocytes was attributed to a decrease in light induced production of ROS, IL8, IL6, TNF alfa, monocyte chemoattractant protein-1, ICAM-1, CCR1 and CCR2.

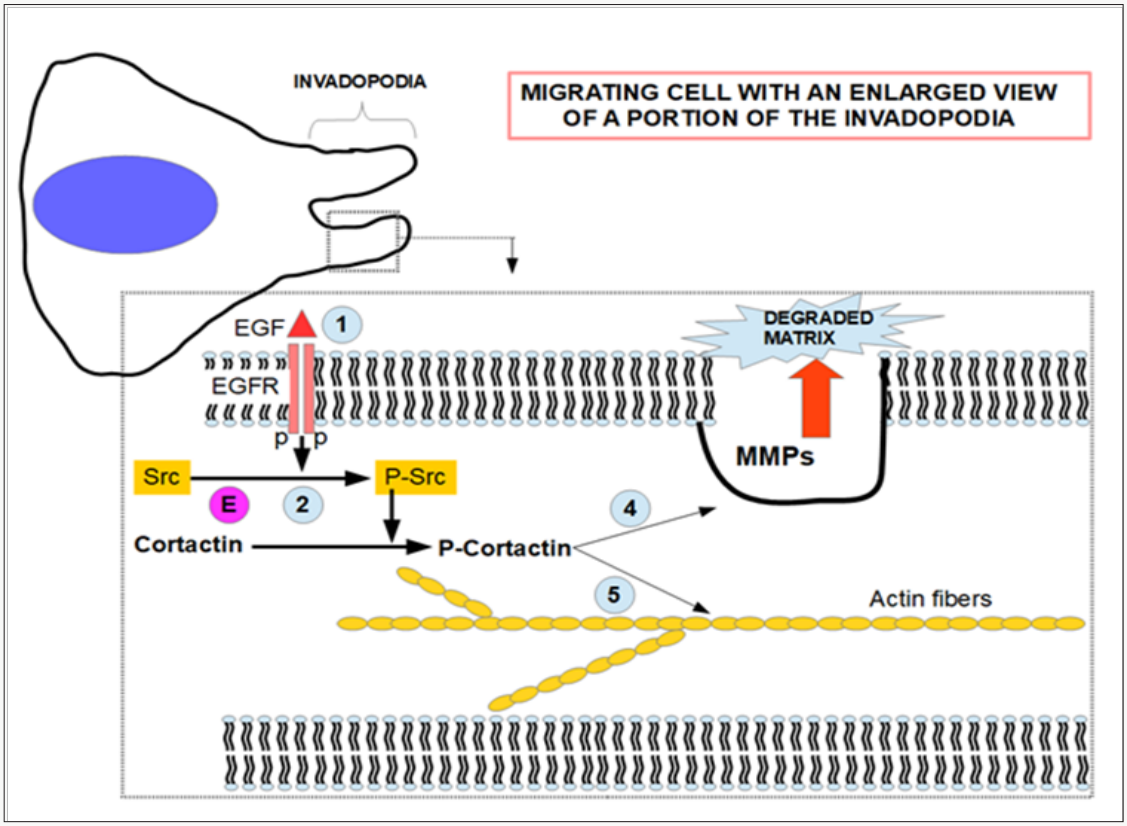

Figure 2: Proposed mechanism for EVO inhibition of migration. References 1) EGF binding and dimerization of the receptor EGFR with phosphorylation; 2) then, it phosphorylates Src; 3) Src phosphorylates cortactin that 4) modulates MMPs secretion and 5) polymeryzes actin fibers. E) site of action of EVO that inhibits Src phosphorylation. Right side of the cell represents the invadopodia. The pseudotubular aspect of invadopodia follows the description made by Brisson et al. [83] in which the extracellular matrix is entrapped in the lumen. NHE-1, VGSC channels and caveolin rafts are also essential structures of the invadopodia that were omitted for a better understanding of the drawing.

The fundamentals for the construction of Figure 2 are:

a. The pathway described by Maders [21] consisting in: EGFR-Src-Arg-cortactin. (Arg was not included in the figure for the sake of clarity. The signal starts at EGFR whether by activation of EGF or by self-activation.

b. The EGF phosphorylation of cortactin is essential for invadopodia formation and maturation [22].

c. Cells treated with either Arg or Src siRNA, showed an important reduction in proteolysis-dependent invasion [21].

d. Cortactin is an important regulator of matrix metalloproteinase secretion [23].

e. Cortactin is a key player in cell migration and invasion [24,25].

f. EVO has the ability to inhibit Src phosphorylation which in turn is an important factor in cortactin activation [26-28].

g. Berberine also has the ability to reduce Src phosphorylation [29]. This is probably the reason why it can act synergistically with EVO in reducing cell motility and invasiveness.

Cell Cycle Arrest

We shall study this effect in different tissues, because the mechanisms involved may differ according to tissues.

a. Breast Cancer: EVO decreased the expression of ER α and β and mediated degradation of ER (estrogen receptors) inhibiting proliferation in MCF-7 and MDA-MB-231 breast cancer cell lines (24). In adriamycin-resistant human breast cancer NCI/ADR-RES cell lines EVO was found to increase tubulin polymerization with G2/M arrest [12].

b. Thyroid cancer: A G2/M arrest was observed when ARO cells were treated with EVO. At the same time researchers found increased expression of cdc25c and cyclin B1 and decreased expression of cdc-p15 [30].

c. Colon cancer: In lovo colon cancer cells the S phase arrest was accompanied by decreased expression of cyclin A and cyclin-dependent kinase 2 and cdc25c [31]. In COLO205 and HT-29 lines the G2/M arrest was accompanied by increased expression of cdc25c and cyclin B1;c-Jun N-terminal kinase (JNK) protein phosphorylation was also increased. JNK activation is a key step for apoptosis [32].

d. Hepatoma: EVO inhibited STAT3 activation, JAK2, Src and ERK1/2. This was accomplished by EVO induced overexpression of shatterproof phosphatase 1 (SHP1) [28]. In SMMC-7721 hepatocarcinoma cell lines, EVO in synergy with berberine produced cell cycle arrest and apoptosis and TNFα was significantly increased [33]. The cell cycle arrest and posterior apoptosis produced by EVO is probably linked to increased nitric oxide (NO) production induced by this drug, interplaying with ROS. NO activates p53 and p21 and finally induce cell cycle arrest and apoptosis. This mechanism was described in melanoma and HeLa cells [34,35] but probably is shared by almost all cells susceptible to EVO's action. The conclusion is that oxidative stress plays an important role in EVO`s cell cycle arrest and apoptosis.

e. Prostate cancer and urothelia: Normal prostate and particularly prostate cancer cells have increased expression of the transmembrane receptor Transient receptor potential vanilloid-1 (TRPV1) [36]. The activation of this receptor (e.g. with capsaicin) decreases the intracellular concentration of calcium. EVO is a TRPV1 agonist (similar to capsaicin regarding this action) [37]. The stimulation of TRPV1 produces a FAS dependent apoptosis in urothelial cells [38,39] and apoptosis in prostate cancer cells [40].

The possible mechanism involved in these actions of TRPV1 is through an increase in ROS [41].

TRPV2 activation also inhibits glioblastoma stem cell proliferation [42].

f. Autophagy: EVO may induce autophagy as a defense mechanism of cell survival, so that its activity in apoptosis is enhanced if it is used simultaneously with inhibitors of autophagy, otherwise EVO may protect cancer cells from apoptosis via autophagy [43].

Anti-anoxia/hypoxia actions of EVO

Hypoxia is an important component of the tumor microenvironment and there is a complex mechanism of adaptation to extreme lack of oxygen through metabolic changes initiated by HIF-1α (hypoxia inducible factor-1 alfa) and the hypoxia responsive elements. Hypoxia and HIF are strong drivers of tumor proliferation and evolution (the analysis of this fundamental issue goes beyond the scope of this article). Any therapy that decreases tumor`s hypoxia or HIF-1α expression may represent a very useful complementary treatment. It has been reported that EVO had strong "anti-anoxic" effects [44]. The anti-anoxic effect of EVO is probably due to two different but complementary actions:

a. Vasodilation: EVO is a powerful vasodilator through the activation of potassium channels in the vasculature and by interference with phosphodiesterase`s degradation of cAMP and cGMP [45].

b. Decreased HIF-1α by regulating its transcriptional activity through dephosphorylation of Akt [46-48].

Effects on angiogenesis

Angiogenesis is a component of tumor expansion and metastasis. In a very early phase of tumor development HIF-1α upregulates the expression of vascular endothelial growth factor (VEGF) which is a driver of new vessel formation. Although these new vessels are highly incompetent from a functional point of view, they play an important role in the metastatic process. EVO has clearly shown anti-angiogenic effects [49,50].

EVO and the vanilloid receptor Transient Receptor Potential Vanilloid-1 (TRPV1)

EVO is an agonist of the vanilloid receptor TRPV1, that is a calcium ion channel activated by vanilloids, protons, heat and several inflammatory mediators. It is i in pain sensing and inflammatory processes [51] and contributes to the regulation of intracellular calcium. TRPV1 is overexpressed in different tumors including breast cancer. Activation of this receptor showed growth inhibition, induction of apoptosis and necrosis in breast cancer in general and in the most aggressive types like the triple negative [52]. The experiments were performed with capsaicin, a TRPV1 activator, but EVO is also an agonist of TRPV1 and acts in a very similar way as capsaicin, so probably the same result could probably be achieved with EVO.

Summary of EVO's effects in cancer

a. Inhibition of migration and invasion probably through Src inhibition.

b. Cell cycle inhibition in the G2/M phase by modulation of cyclins/CDKs

c. Apoptosis and necrosis through many different mechanisms such as oxidative stress, elevation of intracellular ROS and nitric oxide levels, reduction of antioxidant capacity, downregulation of NF-kB, downregulation of HIF-1α and survivin, activation of TRVP1, increasing pro-apoptotic proteins.

d. Anti-angiogenesis.

e. Topoisomerasa I and II inhibition may also play a role in cell cycle arrest and apoptosis [53], [54-58]

Toxicity

No serious studies have been conducted to determine the pharmacokinetics of EVO in superior mammals, or to determine tolerance and toxicity. It is known that it is hepatotoxic at high dose and there is also cumulative hepatotoxicity in mice [59,60]. The Evodia fruit extracts (the source of EVO) are extensively used in China in humans and one case of acute hepatotoxicity has been described with the nutritional supplement White Flood

that contains EVO, but also many other plant extracts including Vinca alkaloids [61,62]. The mechanism of hepatotoxicity seems to be related to oxidative stress and alterations of mitochondrial permeability in liver cells of mice [60]. However the experiments of hepatotoxicity performed on mice used very high doses of Evodia extracts (LD50 = 10g/kg or above) [63] or 50g/kg [64].

Are the clinically achievable concentrations of EVO enough for anti-tumor effects?

A concentration of 10 to 20 μg/ml for 24 hours produces a 70% decrease in migration without modifying tumour growth in vitro. If this concentration is sustained for 48 hours a concentration and time dependent growth inhibition is achieved. Under these experimental conditions the number of lung metastases was diminished by 48% [65]. But concentrations as low as 1.25 μg/ml are sufficient to produce inhibition of migration [10]. MDA-MB-231 cells required higher concentrations to show cytotoxic effects: 30μg/ml for 72 hours produced a decrease in cell viability of up to 77% [8]. We need to keep a concentration around 30μg/ml at tumor level if we want to produce cytotoxicity. Is this possible? The oral administration of EVO in rats has an availability of 0.1% in plasma [66]. Supposing that the availability in humans is the same, we may assume that an oral dose of 1.000 mg would achieve a concentration of 20μg/ml in body fluids.

It remains to be seen if the concentration in body fluids is the same at the tumour microenvironment, because of limitations of blood vessels, and functional insufficiency of the new vessels formed during the process of angiogenesis. It may be presumed that tumour ischemia may play a role in reducing EVO's concentration in the tumour's microenvironment. 1.000mg per os seems a tolerable dose, because many of the over the counter nutritional supplements contain 500 mg of EVO, and some prople take more than one pill a day. Ethanol extracts of EVO seem to produce a higher availability [67,68]. The plasma concentration of EVO peaks within 1 h after oral administration [69]. Wen et al. [70] developed a method to determine body fluids concentrations of EVO, so that it would be relatively simple to test the concentration of the drug in blood. New derivatives of EVO with better availability and better anti-cancer effects are under research [71,72].

Discussion

The lethality of cancer is mainly associated with its ability to produce metastasis. For a metastasis to develop, the cells must be able to migrate and invade. Also metastatic cells need migration as a mechanism to establish themselves in distant colonies. Therefore, reducing migratory capacity should be an essential part of cancer treatment. However, present day oncological treatments pay scarce attention to this issue. If there is a drug with very low toxicity that can substantially reduce migration, it should deserve more attention. There is overwhelming evidence indicating that EVO decreases migration and metastasis in low concentrations and in higher concentrations exerts cytotoxic effects in malignant cells with minimal toxicity for normal cells. There is also evidence that the "anti-migration concentration" is achievable with oral administration.

The cytotoxic effects that require higher concentrations, are not easy to achieve with oral administration and the standard pharmaceutical preparations. This is the reason why more effective pharmaceutical delivery systems are being investigated for this drug. In the event that bioavailability is improved, EVO would be a more potent cytotoxic than paclitaxel [12]. But here, we are limiting our expectations to the anti-migratory effects of EVO. EVO has also shown complementary effects with certain chemotherapeutics like camptothecin in ovarian cancer [57] and erlotinib in NSCLC with non mutated EGFR [58], with doxorubicin [73], with paclitaxel in gastric cancer cells [74], gemcitabine in pancreatic cancer [75], cisplatin in gastric cancer [76,77] and in reversing multi-drug resistance in leukemic cells [78]. EVO`s ability to increase free radicals may also complement radiotherapy, and it has been experimentally tested [79-81]. A combination of evodiamine and nitrogen mustard has been developed; it showed antiproliferative activity without effects on peripheral mononuclear blood cells [82]. EVO and berberine decreased Mir-429 that acts as an oncogene in human colon cancer [83].

But all the above mentioned evidence was obtained in rodents and tissue culture. To the best of our knowledge there are no publications regarding the in vivo activity of EVO in superior mammals and humans. The bioavailability and metabolism in rodents is also well established, but this is not the case for humans. A daily dose of 500 mg per os is well tolerated by humans, as it has been widely used at that dose under the label of "nutrient supplement" for weight loss. It is highly possible that twice that dose would be well tolerated too, and this would make it possible to achieve "anti-migratory" concentrations. The technology for measuring EVO`s plasmatic concentrations is also available. EVO derivatives have been synthesized with increased anti-cancer effects and with lower concentration requirements to achieve cytotoxicity [72].

Another important reason to consider EVO in the anti-cancer armamentarium is its ability to down regulate HIF-1α which is a powerful driver of tumor progression and evolution. Berberine has shown synergistic activities with EVO in cancer cell cycle arrest and apoptosis [84], and the association of these two compounds would make it possible to reduce the high concentrations of EVO needed for its cytotoxic effects. Berberine has its own anticancer effects by inhibiting heparanase`s degradation of the extracellular matrix [85] and thus contributing to EVO`s ability to inhibit migration. The association of these two non toxic drugs may represent an important breakthrough in the battle against migration. The publications mentioned in this review, clearly show that EVO has interesting anti-tumor effects, not only as a "cancer cell killer" but as an inhibitor of migration, invasion and metastasis.

Migration is a complex process in which many proteins participate. Src, inhibited by EVO, is an important player but to really acquire an "anti-migratory condition" other aspects of migration should be dealt with, like NHE-1, VGSCs and the low extracellular pH that favors the activity of proteolytic enzymes. Targeting migration should include an attack on these other players too. Fortunately, there are available drugs that target them: ameloride and its derivatives against NHE-1, anti-epileptics against VGSCs, proton pump inhibitors to raise extracellular matrix pH [86-95]. We believe that associating EVO and berberine with these other anti-migratory drugs may represent a useful partnership. We do not think that any isolated drug, with low toxicity can achieve a significant downturn of migration, but the coordinated association of a few, that act on the different essential proteins required for migration and on extracellular matrix factors like acidity, may do the job.

The complexity of migration is also represented by the fact that there are at least two different forms of migration: mesenchymal and amoeboid. Inhibiting one form of migration may lead to the adoption of the alternative mechanism. But both depend on actin reorganization [96]. Therefore EVO should handicap both types of migration, at least in theory. This needs further experimental confirmation. COX2 is a promoter of invasion and migration [97-99] and metastasis [100]. Celecoxib, a COX2 inhibitor is a modulator of the actin cytoskeleton [101] and an inhibitor of matrix metalloproteinase 2 and 9 [102] so that a synergistic activity with EVO on migration may be expected.

On the other hand, modifying cancer cell adhesion mechanisms may represent an interesting complementary mechanism to "anti-migratory treatment". Celastrol, a natural triterpene inhibits extracellular matrix adhesion of cancer cells inhibiting migration by a different mechanism than that of EVO [103,104], so that it should complement it. A frequent issue in the medical literature is that when the primary tumour is detected, metastases are usually on their way. This "too late" theory should not prevent us from using anti-migratory treatments. Even if it is "too late", primary tumours and metastasis, need migration as an essential condition for local invasion and distant colonization. Metastases need migration to really establish them in the new location. And they also need migration to invade and grow. And there is still the question of metastasis giving rise to new metastases.

Finally, the requirement of high concentrations for EVO`s cytotoxic effects and problems with its bioavailability can be substantially corrected by modifications in sites 13 and 14 of the molecule [105] which would transform it into a new chemotherapeutic drug. Nanoparticle technology may also increase its absorption, concentration in body fluids and cytotoxic effects [106]. Some difficulties in the research of the combination of EVO and berberine have been solved: both can be determined in plasma simultaneously [107]. Using Evodia extracts the absorption of berberine was increased. The activation of vainilloid channels like TRPV1 plays a role in cancer which at the present time is not very clear. Capsaicin is an activator of these channels and at the same time it acts as an inhibitor of VGSCs [108-109]. Blocking VGSCs is a mechanism to decrease the metastatic process [110,111]. EVO is an agonist of TRPV-1 in the same way as capsaicin. It remains to be investigated if it is also a VGSC inhibitor.

The last, but not the least question to consider is tumor hypoxia as a driver for tumor evolution. EVO has shown the ability to reduce the hypoxia response through down regulation of HIF-1α [46]. At the same time berberine targets Sp1 (specifity protein 1) which is a transcription factor for HIF expression [112]. Sp1 is also one of the promoters of NHE-1 [113]. In spite of all the anti-cancer effects of EVO, it increases IL8 expression and adhesive molecules in gastric cancer cells. This may promote metastasis. On the other hand berberine decreased IL8 expression and decreased VCAM-1[114]. Recently, a study of EVO`s possible cardiotoxicity, showed that EVO may be cytotoxic for heart muscle cells in neonatal rats and zebra fish larvae, but there are no studies regarding adult cardiomyocites [115] and there are a diversity of publications showing cardiovascular benefits from EVO [5,116-123]. All this evidence reinforce the concept of the association of EVO and berberine, that allows a lower dose of EVO.

As a summary, and to define cell death pathways and migratory pathways affected by EVO, Table 4 is introduced. This Table 4 pretends to show with more details how the EVO induced cell arrest, through caspase dependent and independent mechanisms, is produced and also the mechanisms behind migration inhibition [124-140].

Conclusion

The importance of migration in tumor development and progression cannot be overemphasized and having a drug like EVO with its low toxicity that may interfere with both, is not a minor fact. Therefore, Evo should be tested in humans to establish the plasma concentrations, because all the published pharmacodynamic reports were based on rodents. Whether alone or associated with berberine, EVO deserves to be tested in well designed clinical trials for the treatment of cancer and prevention of metastasis [141-189].

Future Perspectives

Anti-migratory treatments have not arrived to standard cancer care yet. But most of the required pharmacological resources are almost available. Then, it is only a matter of time and medical "fashion trends" for it to happen. In this case EVO or its derivatives, whether or not combined with berberine, will have a place in anti-migrant treatments. It will possibly form part of a multi-drug scheme against migration, integrated with ameloride derivatives, voltage gated sodium channel blockers, v-ATP-ase proton pump inhibitors and COX2 inhibitors. Certain shortcomings of EVO's bioavailability may be solved with new more soluble compounds or different preparation forms. The almost absent toxicology of EVO at anti-migratory doses make it an ideal drug for this purpose. Even

if EVO's cytotoxic effect is not emphasized in this study, because it requires a concentration that may be difficult to achieve in vivo, it is quite probable that EVO can be developed as a full blown cytotoxic chemotherapeutic drug.

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DOI: 10.32474/OAJOM.2018.01.000111

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