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Letter to the editor:

RECENT DEVELOPMENTS ON POTENTIAL NEW APPLICATIONS OF EMETINE AS ANTI-CANCER AGENT

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Dear Editor,

Cancer remains one of the leading causes of global morbidity and mortality, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 (Stewart and Wild, 2014). Treatment protocols include radiation, surgery, chemotherapy, hormone therapy, immunotherapy and targeted therapy (American Cancer Society, 2015). While chemotherapy is one of the key strategies against cancer, the available drugs are frequently fraught with toxicity and increased frequency of tumor relapse (Gaziano et al., 2016). This calls for an urgent need for more effective anti-tumor agents especially from phytochemicals which are known to be of lower toxicity and cost (Reddy et al., 2003). A wide variety of phytochemicals, particularly alkaloids, have been investigated in recent times in the quest for more effective and safer antitumor agents (Lu et al., 2012; Kharwar et al., 2011). Interestingly, several important antitumor alkaloidal drugs have been isolated from medicinal plants including the vinca alkaloids, vinblastine and vincristine, isolated from the Madagascar periwinkle, *Catharanthus roseus* (Noble et al., 1958; Johnson et al., 1959; Svoboda, 1961) as well as paclitaxel, isolated from *Taxus brevifolia* (Wani et al., 1971). One effective strategy employed by scientists in this regard is the investigation of known drugs for novel biological effects, the so called 'drug repositioning'. One of such known drugs that have been shown to possess anti-tumor activity is the alkaloidal amoebicidal drug, emetine (EMT).

EMT, chemically designated as 2S,3R,11bS)-2-{[(1R)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl]methyl}-3-ethyl-9,10-dimethoxy-2,3,4,6,7,11b-hexahydro-1H-pyrido [2,1-a]isoquinoline (Figure 1), is an isoquinoline alkaloid which occurs in the families of Alangiaceae, Icacinaceae, and Rubiaceae. The major source of EMT and its analogs is *Psychotria ipecacuanha* Stokes (Rubiaceae) which is also known as *Cephaelis ipecacuanha* A. Rich (ipecac) where it is the principal alkaloid (Wiegrebe et al., 1984). It is clinically used (as a dihydrochloride) in the treatment of amoebiasis, a protozoan infection (Vedder, 1912) and it has emetic properties. It is reportedly a protein synthesis inhibitor in eukaryotes (Grollman, 1968). The biosynthesis of EMT and cephaeline (another alkaloid found in ipecac) comes from two main biosynthesis pathways, the biosynthesis of dopamine from L-tyrosine and that of secologanin from geranyl diphosphate (Cheong et al., 2011; Nomura et al., 2010).

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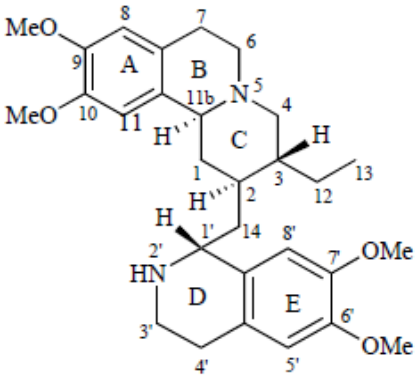

Figure 1: Chemical structure of EMT

The anti-cancer effect of EMT was first reported on malignant human tumors in 1918 by Lewisohn (1918) but since he was unable to reproduce this effect in laboratory animals, he concluded that the drug had no anti-tumor properties and that the tumor regression must have been spontaneous. However, in the following year, Van Hoosen (1919) further reported the remission of various malignancies in a number of patients by EMT. This is followed in later years by reports of effectiveness of EMT in rat Yoshida sarcoma (Isaka, 1950), intra-abdominal and retroperitoneal nonspecific granulomas (Grollman, 1965) and in murine leukemia (Jondorf et al., 1970). Besides, the potency of an analogue of EMT, dehydroemetine, was also shown in chronic granulocytic leukemia (Abd-Rabbo, 1966), various malignancies (Abd-Rabbo, 1969) as well as in Hodgkin's disease and rectal adenocarcinoma (Wyburn-Mason, 1966). Based on these reports, phase I and II clinical trials with EMT were done in the early 1970s (Panettiere and Coltman, 1971; Street, 1972; Mastrangelo et al., 1973; Siddiqui et al., 1973; Moertel et al., 1974; Kane et al., 1975). The drug was, however, discontinued from the clinical trials (Von Hoff et al., 1977) due to its very narrow therapeutic index, cardiac toxicity and other adverse effects which were also observed in the treatment of amoebic patients (Knight, 1980). Since then the drug has been used in *in vitro* experimental studies requiring inhibition of protein biosynthesis (Akinboye et al., 2012). The data from these recent studies have further shown EMT as a modulator of different cancer related biological pathways. In fact, excellent review by Akinboye and Bakare (2011) has shown that EMT exhibits its anti-tumor effect by apoptosis through such mechanisms as inhibition of protein biosynthesis, DNA interaction and regulation of pro-apoptotic factors. In more recent years also, various studies have further investigated the role of EMT in cancer growth arrest and its biological targets using a variety of human carcinoma cell lines. New derivatives have also been synthesized and reported to be efficacious but less toxic to normal cells. Also the drug has been investigated in combination with other agents to assess their anti-tumor synergistic effect which will warrant reduction in its dose. These studies are geared towards bringing back EMT or its derivatives to the clinical limelight in cancer chemotherapy. The present report summarizes these more recent anti-tumor updates on EMT (Table 1). It is hoped that this report will further spur research interests on EMT and its structural modifications towards potential application in cancer chemotherapy.

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Table 1: Recent studies on EMT in relation to anti-cancer effect

Cancer cell line	Studies	Reference
Prostate (LNCaP, PC3), breast (MCF7 and MDA-MB-231) and in normal human prostatic epithelial cell line (PrEC)	EMT was derivatized at its N-2′ position such that it can be selectively delivered as a prodrug to be activated by an enzyme, fibroblast activation protein (FAP) which is selectively overexpressed within the metastatic tumor to cancer cells. Eleven peptidyl EMT prodrug analogs were synthesized and tested for in-vitro activation by FAP. It was shown that one of the prodrugs, a dipeptidyl peptidase-4 (DPPIV) activatable derivative, is activated to EMT (70 % in 24 h) and cytotoxicity studies indicated its equipotence to EMT in the presence of FAP and DPPIV. The prodrug was over 200-fold less cytotoxic than EMT in the normal cell, PrEC cell line.	Akinboye et al., 2016
Prostate cell lines (DU145, PC3 and LNCaP)	Novel EMT dithiocarbamate analogs were synthesized and characterized for anti-tumorigenic activity and minimal toxicity to normal prostate cells. Their targeted apoptotic regulatory genes were also studied. Two key compounds were found to have significant anti-tumor potential in the PC3 cells.	Bamji et al., 2015
Bladder cancer	It was shown that low nanomolar concentrations of EMT completely inhibit expression of HIF1α and HIF2α, but not HIF1β. The decrease in HIFα expression was due to protein synthesis inhibition and also proteasomal degradation. It was suggested that cancer patients may benefit from treatment with a HIFα inhibitor, like EMT given the important role of HIF proteins and hypoxia signaling in promoting tumor growth and progression.	Foreman et al., 2015
Ovarian cancer	Co-administration of cisplatin and EMT not only remarkably induced apoptosis but also reduced the colony formation of the tumor cells. The apoptosis was dependent on the activation of caspases -3, -7 and -8 and downregulation of bcl-xL by EMT.	Sun et al., 2015
Lung cancer p38, ERK and JNK	EMT inhibits migration and invasion of human non-small-cell lung cancer (NSCLC) cells. The drug differentially regulates two (p38 and ERK) out of the three major mitogen-activated protein kinases (MAPKs), p38, ERK and JNK which leads to the selective down-regulation of matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9), two major gelatinases which can degrade extracellular matrix components and allow cancer cells to spread out from its origin.	Kim et al., 2015
Cancer stem cells	A library search of leads having cancer stem cell (CSC) targeting ability as well as the capability of modulating multiple target proteins was done through in silico experiments which screened a number of alkaloids. The findings indicated that EMT and cortistatin have the ability to modulate hedgehog (Hh) pathway. The proposed mechanism is by binding to sonic hedgehog (Hh), smoothened (Smo) and Gli protein which are involved in maintenance of CSCs.	Mayank and Jaitak, 2015
AsPC-1 pancreatic cancer cell	EMT was one of the compounds identified to sensitize the pancreatic tumor cells to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. It was suggested that myeloid cell leukemia sequence-1 (Mcl-1) is involved in pancreatic cancer cell resistance to TRAIL and EMT facilitates the apoptosis of TRAIL-resistant pancreatic cancer cells by specifically inhibiting the protein function of Mcl-1.	Han et al., 2014

Cancer cell line	Studies	Reference
Acute myeloid leukemia (AML) cells	A liposomal formulation encapsulating both daunorubicin (DNR) and EMT was developed for enhanced cytotoxic effect against acute myeloid leukemia (AML) cells to overcome some of the problems of DNR chemotherapy.	Myhren et al., 2014
Bladder cancer	EMT and cisplatin individually and in combined inhibited bladder cancer cell proliferation synergistically primarily by arrest of tumor cell growth rather than by apoptosis.	Foreman et al., 2013
Prostate PC3 and LNCaP	The N-2′ position of the EMT was derivatized to thiourea, urea, sulfonamide, dithiocarbamate, carbamate and pH responsive hydrolysable amide analogs which generally exhibited less cytotoxicity (IC_{50} ranging from 0.079 to 10 μM) than EMT (IC_{50} ranging from 0.0237 to 0.0329 μM).	Akinboye et al., 2012
Human pancreatic (BON-1), and bronchial (NCI-H727 and NCI-H720) cell lines	A study was conducted to study the cytotoxic activity of EMT and CGP-74514A in a three-dimensional model and to study if the mechanism of the cytotoxic activity was induction of apoptosis. The cytotoxic activity was done using an in vitro hollow fiber model while a multiparametric high-content screening assay was used for measurement of apoptosis. The cancer cells tested were human pancreatic carcinoid cell line, BON-1, and the human typical and atypical bronchial carcinoid cell lines NCI-H727 and NCI-H720. Both drugs showed antitumor activity and induced caspase-3 activation indicating apoptosis.	Larrson et al., 2012
Prostate PC3 cells; cervical C33A cells, breast cancer MCF-7 cells and MCF-7/Adr cells	The regulation of the alternative splicing of caspase 9 pre-mRNA was examined in response to EMT hydrochloride. It was suggested that the various splicing patterns of the caspase 9 gene regulated by EMT and other agents may contribute to the resistance or sensitization of the tumors to other cell death inducers.	Pan et al., 2011
786-O cell line, a von Hippel-Lindau (VHL)-deficient clear cell renal cell carcinoma (CCRCC) cell	EMT was identified as a specific inhibitor of hypoxia-inducible factor-2 (HIF-2), protein stability and transcriptional activity. The data from the study support the identification of novel HIF-2 inhibitors through the use of EMT or structurally related compounds as lead compounds.	Kong et al., 2010

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