Medical Review of Medolife’s Escozine™ Technology in Pre-clinical & Clinical data and other Scorpion Venom studies.

ESCOZINE™ is an innovative polarized, potentiated bioactive peptide extracted from the Blue Caribbean Scorpion (Rhopularus Princeps) which contains amino acids, proteins and minerals. Medolife filed a patent in 2012 for ESCOZINE™ and their polarization technology (Patent # US 8,097,284 B2). The polarization technique acts as a delivery system and additionally, amplifies the highly positive charges in the extracellular membrane of in ESCOZINE™. One of the main components of ESCOZINE™, Chlorotoxin (CTX), a 36 amino acid peptide, has a high positive charge at pH 7 and blocks small conductance chloride channels. It also binds preferentially to cancerous or any abnormal cells leaving the normal cells intact.

Mechanistic Mode of Action (MOA):
ESCOZINE™ inhibits blood vessels by the process of angiogenesis in solid tumors. Chlorotoxin blocks trans-membrane fluxes of chlorine and regulates the adjusting of cell growth, cell division, metastasis and induces apoptosis (dose dependent) that leads to tumor cells death. The regulating of activity of the potassium (K+) 3-4 kDa, sodium (N+) 6-8 kDa and chloride (CL+) voltgate ionic channels of the tumor cells leads to growth arrest and causes cell death (apoptosis); additionally, calcium dependent potassium channels inhibit growth of other cancer cells.

The unique polarization technique escalates the highly positive charges in the extracellular membrane in ESCOZINE™, which function as a transportation mechanism. Intensifying the binding preferences to malignant cells and increasing the delivery of ESCOZINE™ specifically to cancer cells by 58%, the polarization amplifies the effectiveness of ESCOZINE™ dramatically compared to a non-polarized compound.

Chemistry Manufacturing Control (CMC)/Formulation:
Alopecil Laboratory, in the Dominican Republic, currently manufactures ESCOZINE® under contractual agreement. In the USA, ESCOZINE® is presently manufactured by Samsun Pharmaceutical in Commerce, CA.

Name: ESCOZINE™
Formulation: Oral solution/dietary supplement
Appearance: Liquid, 120 mL/mg.
Color: Clear transparent
Odor: None
Flavor: None
Conductivity: 75 (μS)
Each bottle contains 120 mL solution
Extract of 67 minerals 0.003 mL
Product is good to use for 12 months at room temperature without refrigeration and 18 months with refrigeration minimally at 2°C-15°C. The product must be kept out of the light.

ESCOZINE™ is registered and approved by the Ministry of Health, Department of Drug and Pharmacies in the Dominican Republic as a Natural Alternative Medicine for oncology therapy. ESCOZINE have been registered in several countries as a neutraceutical drug and registration for other countries ongoing.

ESCOZINE™ is also currently available throughout the world online as a dietary supplement.

Note: Refer to label for additional information and dosing.

Pre-clinical Studies:

A literature search was conducted and yielded many studies that have been done on different species of scorpion venom. Those studies are included in this review as we try to understand the impact of scorpion venom for the treatment of different disease in various therapeutic indications such as oncology, inflammatory and as an analgesic.


ABSTRACT: Scorpion venom toxicity is of major concern due to its influence on human activities and public health. The cytotoxicity and apoptosis induced by scorpion *L. quinquestriatus* venom on two established eukaryotic cell lines (293T and C2C12) were analyzed. Both cultured cell lines were incubated with varying doses (10, 20, and 50 µg/mL) of scorpion venom in serum free medium (SFM) for 0.5, 1, 2, 4, and 8 hours at 37°C. The percentage of total lactate dehydrogenase (LDH) released in the culture during venom incubation was used as an index of cell damage. Control culture was treated with an equal amount of SFM. Cell injury was recognized morphologically and apoptosis was researched by a Fluorescing Apoptosis Detection System using the principle of TUNEL (TdT-mediated dUTP Nick-End Labeling) assay and confirmed by another assay concerning nuclear DNA staining with DAPI stain. Cytotoxicity was remarkable and cell survival highly reduced at the highest tested concentration (50 µg/mL). These effects were rapid and observed within 30 minutes. The apparent initial damage to the nucleus and lysis of the plasmalemma and/or organelle membranes, which was evident by a significant increase in cytosolic LDH release, suggested that this toxin acts at the membrane level. The morphological changes that occurred in apoptotic cells include condensation and compartmentalization of nuclear and cytoplasmic materials into structurally preserved membrane-bound fragments or blebs. The cytotoxic effects are dose and time dependent and cell death by apoptosis was more characteristic of 293T cells than C2C12 cells. The apoptotic effects were more prominent and clear in the early stages of
toxicity, while other forms of cell damage such as swelling, rupture, and/or necrosis occurred at later stages.

Several conclusions can be reached from this study. It is clear that the cytotoxic effects are dose and time dependent, and although *L. quinquestriatus* extract kills cells by different mechanisms, the relationship between these mechanisms is unclear. The apoptotic effects are more prominent and clear in the early stages of toxicity.


ABSTRACT: In Cuba the endemic species of scorpion *Rhopalurus junceus* has been used in traditional medicine for cancer treatment. However, there is little scientific evidence about its potential in cancer therapy. The effect of a range of scorpion venom concentrations (0.1, 0.25, 0.5, 0.75 and 1 mg/mL) against a panel of human tumor cell lines from epithelial (Hela, SiHa, Hep-2, NCI-H292, A549, MDA-MB-231, MDA-MB-468, HT-29), hematopoietic origins (U937, K562, Raji) and normal cells (MRC-5, MDCK, Vero) was determined by the MTT assay. Additionally, the effect of venom on tumor cell death was assayed by Fluorescence microscopy, RT-PCR and western blot. Only the epithelial cancer cells showed significant cell viability reduction, with medium cytotoxic concentration (*IC*₅₀) ranging from 0.6-1 mg/mL, in a concentration-dependent manner. There was no effect on either normal or hematopoietic tumor cells. Scorpion venom demonstrated to induce apoptosis in less sensitive tumor cells (Hela) as evidenced by chromatin condensation, over expression of p53 and bax mRNA, down expression of bcl-2 mRNA and increase of activated caspases 3, 8, 9. In most sensitive tumor cells (A549), scorpion venom induced necrosis evidenced by acridine orange/ethidium bromide fluorescent dyes and down-expression of apoptosis-related genes. We concluded the scorpion venom from *R. junceus* possessed a selective and differential toxicity against epithelial cancer cells. This is the first report related to biological effect of *R. junceus* venom against a panel of tumor cells lines. All these results make *R. junceus* venom as a promising natural product for cancer treatment.

**Preclinical Pharmacodynamic Studies on the Activity of ESCOZINE™ and / or Derived Peptides in Primary Leukemia Cells from Patients with Chronic Lymphocytic Leukemia (CLL) and Cancer Cell Lines (NCI-60)*** (UCSD Moores Cancer Center Blood & Marrow Transplantation Division, San Diego, CA sponsored by Medolife).

* The National Cancer Institute (NCI) uses the in vitro human tumor cell line assay, which consists of 60 different cancer cell lines. The NCI-60 cell lines include the following cell lines:

**COLON:** HT29, HCC-2998, HCT116, SW620, COLO205, HCT15, KM12
**BREAST:** MCF7, MCF7ADRr, MDAMB231, HS578T, MDAMB435, MDN, BT549, T47D
**OVARIAN:** OVCAR3, OVCAR4, OVCAR5, OVCAR8, IGROV1, SKOV3
**LEUKEMIA:** CCRFCEM, K562, MOLT4, HL60, RPMI8266, SR
Primary leukemia cells from patients with chronic lymphocytic leukemia (CLL) or cancer cell lines (Human Chronic Myeloid Leukemia, Human Chronic B Cell Leukemia, Human Burkitt Lymphoma) were incubated in RPMI media supplemented with 10% fetal bovine serum (FBS) and 1% antibiotics. The cells were incubated at 37°C for 48 hours in 96-well round bottom plates with different compounds using the concentrations. Escozine incubations were performed using three separate lots of various concentrations. All of the batches were tested using a variety of both leukemia/lymphoma cancer cell lines as well as primary leukemia cells from CLL patients. Apoptosis was measured by Propidium Iodide (PI) and 3,3′-dihexyloxacarbocyanine iodide (DiOC6) staining and flow cytometry analysis.

The results indicated cell death was observed in all cell lines when treated with Escozine (ESCZ) after 48 hours of incubation at 37°C. The effect on cell death (apoptosis) was dose dependent across all cell lines with insignificant cell death observed at the 10% and 30% concentrations. A concentration of 50% ESCZ had a varying range of specifically induced apoptosis (SIA) from 5 – 40% depending upon the cell line. A concentration of 100% ESCZ had a varying range of specifically induced apoptosis (SIA) up to 95%, depending upon the cell line.

**Evaluate the Chemo sensitization of Escozine in Combination with Different Chemotherapy Agents for the Induction of Apoptosis in various Cancer Cell Lines.**

The chemo sensitization effect is determined after incubating each cell line with different concentrations of Escozine, other chemotherapeutic agents, and combination of Escozine and chemotherapeutics agents such as Cyclophosphamide (4-HC), Etoposide (ETO), Cisplatin (CDDP), Fludarabine, Bendamustine (BEN) and Rituximab (RTX). A synergistic effect means the compounds induce greater apoptosis when given together than the total effects of both compounds alone (the observed effects in combination shown to be more effective). To evaluate the combined levels of apoptosis (Escozine + chemotherapy), a concentration of 50% ESCZ was used to induce a moderate amount of SIA across almost all cell lines and CLL patients.

**Interpretation**

Cell death (apoptosis) were observed in all primary leukemia cells or cell lines when treated with chemotherapy, Escozine (ESCZ), and chemotherapy plus 50% Escozine after 48 hours of incubation at 37°C. Different concentrations of chemotherapies were used depending upon the cell line to ensure a full range of cell death was observed (both low and high SIA).

**Note:** For more details on all cell line studies conducted by Moores Cancer Center, please refer to the “Final Study Report” dated March 12, 2012.
Clinical Studies:

Cuban Study:
ESCOZUL has three fundamental properties demonstrated both preclinical and by the medical evidence for cancer, analgesic and anti-inflammatory. It has been released to the public because the results obtained with cancer patients are really promising and does not cause side effects.

The following information is a summation of an eight-year third stage clinical trial sponsored by the Cuban company, Labiofam. In this study, 8,302 patients representing a wide spectrum of cancer types and severities were treated with ESCOZUL (blue scorpion serum).

The most common advanced malignancies studied were in breast, brain, lung, prostate and colon. Laryngeal cancer, lung cancer and cancer of the uterus showed the best results in the study. In addition, for the three types of cancer, which were the focus of the report (larynx, lung, and uterus), 64.6% of the patients in this study had a score of between 60 and 100 on the Karnofsky scale. This means that 64.6% of patients were able to maintain a relatively or completely normal life after taking the serum for a period of six months.

Pharmacological Evaluation
Most patients treated with the concentrated drug present breast (23.44%), prostate (17.86%), lung (8.87%), colon (8.72%) and brain cancer (8.21%). There is a large registry of the positive effects of ESCOZUL in cancer patients. More than 25,000 patients have reported an improvement after having been treated with ESCOZUL, even people to whom conventional therapy had not offered any improvement. From a clinical point of view, 90% of the patients have shown an improvement in their quality of life 2 or 3 months after starting the treatment, resulting in returning or improvement of appetite, decreased inflammation and significant decrease in pain, which allows the patient to the return to normal life. Treatment effects are manifested gradually and depend on the venom concentration that is applied according to the patient's health status. Some indicators that the medicine is working include: decrease of pain and increase in appetite and no problem sleeping, a significant improvement in the quality of life. After some time of treatment it is observed a decrease in the metabolic activity of the tumor and decreases of tumor markers, which shows the antiproliferative activity of the drug.

Evaluation of the toxic effects of venom
ESCOZUL does not cause any toxic side effect when taken orally. In mice study, multiple doses of ESCOZUL given (0 mg/Kg, 5 mg/Kg, 50 mg/Kg y 300 mg/Kg) orally for 14 days and adverse effects observed at the highest dose of 300 mg/kg were motor function, reflex, convulsions, salivation, sedation, somnolence, skin condition, mucosa, eyes and other organs. There was no mortality, weight loss or alteration of the internal organs. On the other hand it was observed sedation, a light locomotion slowdown and a reflex reduction. Based on the 14 days toxicology study ESCOZUL is quite safe for oral administration. (Labiofarm Clinical Study).
**Interventional Clinical Study sponsored by Medolife:**

Primary Investigators: Ramón Feliz, MD; Oncologist/Surgeon
Salvador Vargas, MD; Clinical Oncologist

Study Design: Allocation: Randomized
Control: Uncontrolled
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Open Label

Primary Purpose: Treatment for advanced malignancies (Pancreatic Adenocarcinoma (head of the pancreas), Breast Cancer, Carcinoma of Colon with metastatic recurrent in liver, Recurrent Colon carcinoma metastatic to liver, Lymphoma no Hodgkin Stage IV-A, Pancreatic Carcinoma, Recurring rectal cancer, Endometrial Adenocarcinoma invading the uterine)

This study was an open label randomized study developed to evaluate the effectiveness of POLARIZED SCORPION VENOM (PSV) and its safety, time to disease progression and survival rates after treatment.

Dosing regimen: Investigational medical product (IMP) of 0.5 to 1cc given 3 to 4 times a day of PSV for 3 months or more

Patients will undergo baseline and follow-up clinical examinations including Magnetic resonance imaging (MRI), CT Scan, Mammography, PET Scan, routine blood and tumor marker testing during the conduct of the study.

**Primary Outcome Measures:**
- Determine Maximum Tolerated Dose (MTD) of POLARIZED SCORPION VENOM (PSV) administered orally.
- Determine the toxicity of POLARIZED SCORPION VENOM (PSV) from 0.25 mL up to 1mL dose administrations.
- Evaluate the rate of progression and survival of patients. [Time Frame: at 3 month intervals from first dose administration, until disease progression]
- Evaluate the overall time to progression and death of patients [Time Frame: at 3 month intervals until disease progression]

**Secondary Outcome Measures:**
- Evaluate if POLARIZED SCORPION VENOM (PSV) affects Quality of Life [Time Frame: 3 month intervals until disease progression]

**Eligibility:**
Ages Eligible for Study: 2 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No
Inclusion Criteria:

- Patient must have cancer progression or recurrence following chemotherapy radiotherapy, hormone therapy, and surgery.
- Patient must have recovered from toxicity of prior therapy.
- Patient must be > 2 years of age.
- Patient has a Karnofsky Performance Status greater than or equal to 60%.
- Patient must have a life expectancy of at least 3 months.
- Patient has no uncontrolled conditions that would interfere with evaluation.

Exclusion Criteria:

- Patient with the potential for pregnancy or impregnating their partner and who do not agree to follow an acceptable birth control method to avoid conception.
- Pregnant or breast-feeding females.

Results:

- We compared the results every month and observed that the levels of the serum tumor markers (CEA, CA-125, CA19-9, CA15-3, PSA) decreased gradually.
- In some cases, significant decrease of circulating cancer antigen in serum from 52 to 33ng. Also, observed from the fourth to the sixth day, the intensity of pain was also decreasing. From the sixth to the tenth day the physical conditions of the patients and their physical energy significantly improved.
- After a month of the administration of Polarized Scorpion Venom (PSV), a slight decrease in the circulation cancer antigen confirmed by tumor markers assay and an improvement in the patients' Complete Blood Count (CBC) were observed.
- In the second month of image/scan control, observed that the tumor continues to decrease in size as well and the serum tumor marker levels in both men and women.
- It was observed that the combination use of Polarized Scorpion Venom (PSV) with chemotherapy produced better results in the decrease of serum tumor markers, and the patients showed less weakness in the subsequent days after starting the treatment than did those who used only one of the two treatments.
- Based on the observed results, we recommend the use of Polarized Scorpion Venom (PSV) in combination with chemotherapy as additional option for cancer treatment.

Secondary Effects: No signs of allergic reactions were observed in any part of the body, or vital signs. The patients showed good tolerance to Polarized Scorpion Venom (PSV) and did not develop any complications, nor did any patients die during the conduct of the study.

Conclusion: The observation of the administration of Polarized Scorpion Venom (PSV) orally in patients diagnosed with advanced malignancies, during observation period, showed an improvement in the following areas:

1. Decrease of the serum tumor marker levels
2. Decrease of tumor size
3. Improvement of patient’s clinical condition, quality of life
4. Decrease in size of the tumor and metastasis
5. There were no signs of toxicities in any of the patients clinically observed in the duration of the study.
6. None of the patients developed any complications. The Polarized Scorpion Venom (PSV) dosage was well tolerated when administered during both clinical studies, including data from publications and patients testimonials. There were no deaths reported during the clinical studies in relation to Escozine therapy.
7. The decrease of tumor and the patient’s general clinical condition were observed with Polarized Scorpion Venom (PSV) in combination with other chemotherapy than in those patients who used only one of the two treatments.

This study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312, and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements.

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Abstract/Publication

Cancer Pain Management with Venom of Blue Scorpion Endemic in Cuba Called Rhopalurus junceus “Escozul”. Di Lorenzo L.¹, Palmieri Chiara², Cusano Antonio¹ and Foti Calogero¹
¹Rehabilitation Unit Rummo BN Hospital Doctorate Program, Rehab Med Tor Vergata University, Rome, Italy
²Campus Biomedico Oncology, University of Rome, Rome, Italy

Abstract: During the management of cancer pain sometimes patients ask for alternative, unusual, non-recognized approaches. Last year we followed a cancer patient treated with an active substance that is the venom of blue scorpions endemic to Cuba, called Rhopalurus junceus (“Escozul”) that experienced an unexpected total pain relief with a good recovery of muscle strength, vital energy and capacity to cope with daily activities such as meal, walking and interacting with relatives and caregivers.

This 69-year-old Caucasian male patient had a partial gastrectomy in 2005 for a gastric cancer. Late in 2009 he had a diagnosis of inoperable cancer relapse in stomach fundus with several hepatic metastasis. In January 2010, with a Pain Visual Analogical Scale of 7 out of 10, he started pain management with opioid. In August 2010 he received escalation doses of Fentanyl patch 50 mcg die, morphine and NAIISDs as needed. In September relatives asked about Escozul therapy surprising us because we did not know anything about it.

Escozul is, unfortunately, a product that is still under clinical investigation only in Cuba. It has been released free of charge to all worldwide patients until 2011. Cuban results are available on the internet.
Our patient did take Escozul and started to take it on 9th of October 2010. After 18 days he was able to stop opioid and he did not take any pain killers from November to the last week of February 2011. From October 2010 to February 2011 he achieved an unexpected good pain relief with an effectiveness of about 90% (Pain VAS of 7.5 was reduced to Pain Vas of about 1.5.)

His hematological data were already surprising and patients reported also an unexpected reduction of prostate-specific antigen (PSA) that was higher for a benign prostatic hyperplasia; patient experienced a reduction of PSA value from 335 ng/mL to 54 ng/mL in only 1 month. Tumor Markers CEA, CA19-9 and CA125 in monitoring of response to systemic chemotherapy were also significantly reduced to more than 50%. What was really astonishing in this patient was that venom did not seem to change the tumor status as reported in the CT scans performed during follow up, but the patient experienced an unexpected total pain relief with a good recovery of muscle strength, vital energy and capacity to cope with daily activities such as meal, walking and interacting with relatives and caregivers. He did not experience any side effects until the end of February. He died in March 2011 from a sudden myocardial infarction without any evidence of poisoning. This was an unexpected death probably due to a following classic arrhythmia.

Case Studies:

A case study presented by health care provider, Dr. Alisher Kasimov. A 19-year-old male patient from Uzbekistan was diagnosed with medulloblastoma (brain tumor) in 2008. Medical history included radiation therapy for lumbar spine metastasis (04/2011-12/2012), including reported of evidence of lumbar metastasis on 02/2013, confirmed by MRI scan.

On 24JUN2011, due to recurrence of the medulloblastoma cancer, the patient underwent surgery at the neurological clinic in Yekaterinburg (Russia) for a resection media sub occipital craniotomy procedure removing relapse 4th ventricle in the cerebellar hemispheres. Other procedures including trepanation and ventriculocisternostomy. Histological biopsy result was medulloblastoma poorly differentiated. On 10SEPT2010 the tumor size was 33-20-18mm, then on 05SEPT2011 was 34-18-22mm.

On 07NOV2011 to 12DEC2011, the patient received 2 cycles of Post cycle therapy (PCT) of (Cisplatin 40mg days 1-4 SD-160mg, etoposide 150mg days 1-4 SD-600mg, vincristine 2 mg day 1). Then on 05 JAN 2012, a scan of the tumor showed no effect 4.5 x1, 4x3, 0 cm.

On 05MAR2013, the patient was started on Escozine orally of 1ml 4 times daily and nasal drops of 0.12 ml in each nostrils, 4 times day. After 3 months of taking Escozine, the tumor size was slightly decreased from 4.5 x1, 4x3, 0 cm to 4.0x1.4x2.8 cm 04.06.2013.

After 4 months of Escozine therapy, a multi-slice computer tomography (MSCT) showed no recurrence of the tumor in the projection of the cerebellar vermis postoperative irregularly shaped cavity, which communicates with the fourth ventricle, surrounded by a zone of gliosis and atrophic changes. Common cavity dimensions 4.0x0.9x2.8 cm cerebellum signs of atrophy. However, the patient developed symptoms of spinal manifestations of MRI in the form of compression (pathological) fracture
bodies L1, L3, L5 vertebrae including steochondrosis of the lumbosacral spine. Additionally, movement and sensitivity restored, the patient began to walk and use both hands and legs. (Reference: Patient hospitalization records provided by HCP).

**Medical Review Discussion:**

1. **ESCOZINE™** shows inhibition and apoptosis in various cancer cell lines.
2. **ESCOZINE™** demonstrates a synergetic effect in combination with various chemotherapy drugs.
3. **ESCOZINE™** shows a specific binding preference to cancer cells and possibly disrupt the ion channels intra-cellular activity without affecting the naïve cells.
4. Additionally, studies conducted using other species of scorpion venom demonstrated similar cellular effect of apoptosis using different cancer cell lines.
5. In case studies and abstracts provide supportive evidence of tumor decrease, anti inflammatory and analgesics in patients using Polarized Escozine.
6. In the clinical setting and testimonials from patients demonstrated efficacy and safety and/or minimal side effects such as vomiting, nausea etc.
7. No Serious Adverse Effect reported in the clinical studies conducted in the Cuba or Dominican Republic.
8. The Blue Scorpion Venom with Medolife Polarization technology appears to be safe and efficacious specifically for indications such as anti-tumor, inflammation and pain.
9. However, moving forward Medolife and its Partners will be conducting much more robust randomized clinical study in accordance to ICH guidelines in preparation for Regulatory Registration.
10. Escozine in combination with other natural products are in development for wellness (alternative medicine) and to improve quality of life.

Date: 01/12/2014

Vivek Ramana, MD
President & CEO
InnoVision Therapeutics Corporation