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Exploitation of Snake Venom and its components for Cancer Therapy- A Note

S Paulraj[1], K Ramalingam[2], V Kalaiarasan[3], G Sarvanan[4] and Babu K[5]*

[1]*IFS Retd, Executive Chairman, Snake Park, Chennai, Tamil Nadu, India*

[2]*Senior Project Scientist, Snake Park, Chennai, Tamil Nadu, India*

[3]*Director Research and Development, Snake Park, Chennai, Tamil Nadu, India*

[4]*Research Head, Erode Cancer Centre, Erode, Tamil Nadu, India*

[5]*P G and Research Dept. of Zoology, Arignar Anna Government Arts College, Tamil Nadu, India*

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Corresponding author: K Ramalingam, Senior Project Scientist, Snake Park, Chennai, Tamil Nadu, India

Abstract

Conventional therapies for the disease cancer involves 3 modalities viz. chemotherapy radiation and surgery. The complete 100 percentage cancer cure could not be accomplished due to individual variable potentials and resistance to endure the side effects. Hence oncological experts still strive hand to achieve by novel drugs derived from various sources such as plant, animals, and synthetic products. Towards this, the cytotoxic components of the snake venom to eradicate the complete malignant cells in the primary sites as well as in the secondary metastatic sites/ organs. The snake venoms being a conglomeration of various mixtures of different proteins, enzymes, metals, and toxic enzymes that act as either hemotoxic or neurotoxic, and their properties seem to be a promising agent to kill the cells through their differential functions, such as seizing tumour growth, inhibition of biochemical pathways that promote carcinogenesis, inhibition of certain signals for specific enzymes and protein factors that cause the synthesis of onco-proteins, prevention of epigenetic expression of cancer genes, and promotion of apoptotic genes. Still, we must go a long way in tackling the above disease. Unravelling the cytotoxic potentials snake venom organic compounds would prove to be a superior to the synthetic drugs in the war against cancer.

Keywords: Snake venom; Hemotoxin; Neuro toxin; Tumour; Metastasis; Inhibition

Opinion

Considering the theme Minimize Harms and Maximize Benefits for cancer cure [1] the exploitation of snake venom may seem untenable and / or as an abuse in view of the poisonous composition of snake venom with several enzymes, non-enzymes toxic peptides low molecular weight and high molecular weight proteins and also their impact on blood parameters and neural network of the envenomed patients or individuals. Among the various bio-active substances in the venom, matrix maltallo Proteinases (SVMMP ase), L- amino acid oxidases (LAAO) and a phospholipase A2S (PLA2) are malicious. The peptides and proteins account for 95% of snake venom dry weight while the rest 5% comprises the lipids, carbohydrates and biogenic amines.

The metallo proteinases (SVMP) and serine proteases are most abundant in the venom. Thromobo cytopenia and hypofibrinogenemia are the deleterious outcome of hemostatic disturbances by the snake venom's. SVMPs, SVSP, PLA2, C-type lectins, L-AAO, Hyaluronidase are the toxic proteins which can induce inflammation, oxidative cum nitrative stress, thrombo cytopenia coagulopathies and bleedings etc. in human Cancer constitutes a multiple etiological disease caused by several environmental factors, with genetic malfunctions of normal cellular metabolism due to the cumulative addition of mutations to the extent of more than one lakh [2]**.** The life style factors represent the second most important cause of carcinogenesis especially in the economically developed countries like USA and Europe. According to the International Agency for Research on cancer it represents a malicious disease affecting more than 10 million individuals annually. WHOs futuristic estimation revealed that by 2030, cancer will cause 13.1 million deaths per annum [3]. The delineation of the disease characteristics which are the hallmarks to diagnose cancer has been made by several investigators in oncology. The chemotherapy, Radiation therapy and surgery are the three modalities of cancer treatment in existence as of now. The advancements made in these conventional strategies have

made great strides in gaining control over the disease clinically.

The salient features regarding the success of orthodoxic/ conventional therapies include the following The diagnosis of early stages of cancer (stage 1 & 2).

i. The cure rate in overall cancers has increased markedly in the recent decades beyond 2000

ii. Treatment has become more individualized.

iii. The genomics has identified the high-risk groups and the familial cancers (hereditary)

iv. The immuno therapeutic approach and adjuvant therapies combined with the regular chemotherapy have been developed as alternative approaches to revamp the suppressed immune cells in vivo of the disease afflicted individuals.

Despite the advancements in the treatment strategies in conventional therapies the challenging feats for clinicians and oncologists regarding cancer disease entities are the following

1. The emergence of side effects consequent to all the three modes of treatments.

2. The problem of malignant cells indifference and resistance to drugs

3. Declining immunity in cancer patients

4. Drug related deaths.

5. Incompatibility of the results obtained in tissue culture in vitro in clinical practice and limitations *in-vivo.*

6. Arousal of malignant cells after remission period with more resistance to drugs

7. The mechanisms to switch off the functions of oncogenes or cancer genes that turn on the carcinogenesis process has not been identified.

In cancer therapy, despite extensive research on chemotherapy, development of new drugs without side effects as seen in conventional strategies, are warranted. Toward this snake venom promises to have a great potential as an anti- cancer agent and recent research investigations have elucidated that the peptides and enzyme components can cause deleterious effect to the cancer cell membrane and/ or interfere with the transport of substance which are cancer growth factors and interfere signal transduction processes in cancer cells which cause their proliferation and metastasis. Pharmaceutical domain views that the snake venom could open the doors for the new era of medicine in the treatment of cancer.

To form an oncological basis for the use of snake venom in cancer therapy, some preliminary observations in our school Ramalingam et al. [1] were made regarding the presence of venom in the different tissues of the victim (mice) subjected to envenomation (animal model) [4]. The result of the present investigation reveals the short duration of bringing mortality to mice by the Cobra (*Naja naja)* venom i.e., within 1 to 12 hrs. maximum in a median lethal dose of 13 µg/ kg weight. The venom was detected in all organs, irrespective of its specificity as a neurotoxin. The venom was detected for up to 3 hours in the tissues. The above findings construe that the naja venom showed a homogeneous diffusion in different organs. The venom poisoning effect extends up to three hours only. Since all the vital organs are absorbing the venom, the death due to envenomation may be attributed to the multi organs lethal toxicity and failure of multi organ's function.

The pathological results imply that the poisoning would have brought damage to the brain and its neural network. In blood the hemolytic effect could have taken place and in the heart, the cardiac muscle may have been impaired. Likewise, the spleen poisoning may have brought the immuno depression and death of the immune cells in the animal. The results infer the high cytotoxicity of the venom in mice which may constitute the basis for the drug designing and bio similar drugs development, like the derivation of some anticancer compounds from the plants like vincristine, vinblastin, vinorbine, epipodophyllotoxin and taxols etc.

The result also revealed the uniform diffusion potential of the venom in different organs. As metastasis constitutes a critical process of spread of malignant cells in different organs like brain, Liver, Peritonea, Ovary, Uterine-cervix, bones, the drugs, or the components of venom with equal potential of diffusion constant may help to destroy the invasive metastatic cells and their establishment of secondary cancer cell populations, in the distant organ. This could be secondary breakthrough accomplishment in targeted therapy as drug in combination with bio active metabolites of plants can destroy the malignant cells in systemic circulation before seeding to distant organs as well as in the organs where the cells have been seeded.

The subtle mind-blowing query that remains is in the exploitation of snake venom, the deadliest poison towards cancer treatment. In this context, several research investigations recommended the usage of individual components and/or enzymes towards that end. For instance, studies have revealed that cobra snake venom's cardiotoxin 3 (CTX 3) revealed its potential to decrease the expression activity of MMP ase-9 and the inactivation of MAPK and P13^{1c}/ AKT signaling pathways and NF-KB activity in the metastatic breast cancer cells.

Botrhops pauloensis, Botrhops. diporus and *Botrhops. pirajai venoms* which consist of the parts of pharmacologically active biomolecules, have been analysed against the cell lines HCT-8 (colon), HL-60 (leukaemia), MDAMB-435 (breast), and SF-295 (nervous system) and results showed high therapeutic potential effects such as anti-angiogenesis, inhibition of protein synthesis, necrosis, and apoptosis [5,6].

Similarly, the Russell viper *Daboia russelii siamensis* venom has

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an active compound enzyme, the phospholipase A_2 superfamily, which consists of five distinct enzymes among 15 groups of crude protein venom has shown anti-cancer effects on human urinary bladder carcinoma (T24), human lung bronchus carcinoma (ChaGo-K-1), human fibrosarcoma (HT-1080), human skin melanoma (SK-MEL-28), and murine skin melanoma (B16F10). One of the compounds in phospholipase A_2 (Drs-PLA_2) inhibits tumor colonization through the prevention of nodule formation, migration, and metastasis Khunsap et al. [7].

Juhl et al. [8] have revealed that the cardiotoxin of the cobra venom inhibited the nucleic acid synthesis and decreased the cell proliferation in breast cancer tissue. Cytotoxic effects of cobra venom components were also reported against human lung adenocarcinoma A549, and promyelocytic leukemia HL60 and Ehrlich as cites tumors cells. (de Vieira Santos et.al. [9]; Feofanov et.al. [10]. Bazaa et.al. [11] have reported that snake venom's PLA_2 inhibited angiogenesis through an increase in the microtubule dynamics and disorganization of the focal adhesions. Bharathirajan et al. [12] also have revealed that $CaCl_2$ added cobra venom showed significant loss of SP^2/O myeloma cells. The cancer cells death was attributed to the probable disruption of the cancer cell membrane and the consequent influx of Ca^{2+} into the cytoplasm to cause cell death. Mora et al. [13] have opined that the cancer cellular proliferation response depends on a regulated Ca^{2+} influx through the plasma membrane. Wide spectrum of cancer types cytotoxically affected by the individual components of snake venom becomes evident and proves to be a prudent approach for the cancer therapy [7,19]. It is also opined by Jorge et al. (2011) that molecular model for synthesizing synthetic drugs mimicking the action of snake venom components would be of immense value in cancer treatment [14-19].

Conclusion

The above findings are evidence to the concepts in the cancer target therapy that the snake venom components need further advances for the isolation and purification of specific targeting ligands alongside specific plant bioactive molecules would be promising to yield results which will pave way to designing of a novel synthetic anti-cancer chemotherapeutic drug which would be effective to bring cytotoxic death to cancer cells without showing the side effects to the patients.

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