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Applications of snake venoms in treatment of cancer

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ABSTRACT

Snake venoms are folk medicines used since ages. The components of snake venoms have high specific affinity and actions on cells and cell components. Also snake venoms are largely cytotoxic to tumor cells than normal cells. In addition to these, they have several therapeutic actions that make them an attractive option in the management of cancer. The advent of modern technologies has greatly helped in extracting and identifying new components of therapeutic interests in short time. The article highlights the importance of snake venoms in the management of cancer, so as to motivate curious researchers to devote their skills in this fascinating area. This in turn may bring hope, smile and relief to several cancer patients in future.

1. Introduction

Snake venoms have the highest toxicity potential that makes them an attractive option in the development of anticancer agents. Evolution of modern high throughput screening systems has helped to recognize and extract new therapeutic substances from biotoxins such as venoms of several snakes that show promising potential to combat cancer. Growing understanding of molecular mechanism is also contributing in this direction[1].

Snake venom is a complex mixture of enzymes, peptides, carbohydrates, minerals and proteins of low molecular mass with specific chemical and biological activities[2,3]. Components of snake venoms can be used in the treatment of cancer, arthritis, thrombosis, multiple sclerosis, pain, neuromuscular disorders, blood and cardiovascular disorders, infections and inflammatory diseases[1-3]. Snake venom contains cytotoxins, cardiotoxins, hemotoxins, neurotoxins, nerve growth factor, inorganic cations like zinc, calcium, potassium, sodium and magnesium, *etc*. Phospholipase A_2, ancrod, cobra venom factor, peptides, cytotoxins CT1, CT2 and CT3, crotoxin, L-amino acid oxidases (LAAOs), lectins, metalloproteinases, disintegrins, serinoproteases, hyaluronidase, cholinesterases, salmosin, cathelicidin-BF, aggretin, obtustatin, rhodostomin, albolabrin, colombistatin, saxatilin and lebecetin are some of the components isolated from various snake venoms, which show promising applications in management of various human cancers. Several researches have been conducted on actions of snake venoms on tumor cell cultures and some of them are in phase I and phase II clinical trials[3-6].

Disintegrins, like contortrostatin isolated from *Agkistrodon contortrix* venom prevents cells from adhering together and inhibits their interaction with surrounding tissue, resulting in decreased cell motility and invasiveness[1]. Cytotoxic effect of snake venom has potential to directly destroy tumor cells. Fibrin deposition around tumor could form a protective barrier, but also prevent tumor progression. Also fibrin deposits formed by metastatic tumor cells may help disseminating these tumor cells. Snake venom containing ancrod, a polypeptide can produce defibrination and decrease spread of some tumors[1,3,4]. C-type lectins inhibit integrin-

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dependent proliferation, migration, invasion, and angiogenesis. C-type lectins have been isolated from *Macrovipera lebetina* snake venom. Secreted phospholipases A_2 ($sPLA_2$) isolated from *Cerastes cerastes* and *Macrovipera lebetina* have promising antitumor and antiangiogenic properties since they act specifically on integrins α5β1 and αβ[7]. Also $sPLA_2$ from *Daboia russelii siamensis* venom shows cytotoxic effect and inhibits cell migration in human skin melanoma cells. It also reduces tumor lung colonization of B16F10 melanoma cells in BALB/c mice. $sPLA_2$ has anticoagulant properties which may prevent recurrent thrombosis, which is the second most common cause of death in cancer patients[8].

2. Snake venom components

Snake venom containing cystatin decreases tumor invasion and metastasis. Snake venom components can be specifically directed to cancer cells by combining the components with nanoparticles[5]. Cobra venom factor is an important factor for the synthesis of immunoconjugates, which are more specific towards carcinoma cells[3]. Cobra venom in very minute doses has powerful analgesic activity than morphine and can reduce intractable pain associated with cancer[1,2]. The enzyme LAAOs isolated from snake venoms induce apoptosis, alterations in cell cycle processes and cytotoxicity and have promising potentials in development of new antitumor agents[9,10]. Production of hydrogen peroxide during enzymatic reaction, caspases activation and interaction of LAAOs with membrane receptors are some of the possible mechanisms behind the actions of snake venom LAAOs[10].

Snake venom components basically inhibit cell proliferation and promote cell death. Mechanisms of action include: increasing calcium ion influx, inducing cytochrome C release, increasing or decreasing the expression of proteins that control cell cycle, inflicting cell membrane damage, anti-platelet action preventing fibrin formation, preventing thrombin induced metastasis, inducing cancer cell apoptosis thereby controlling tumor size, direct toxicity and free radical generation, inhibiting nucleic acid synthesis thereby suppressing cell proliferation, decreasing the expression and activity of matrix metalloproteinases, inhibiting integrins thereby preventing migration and invasion of cancer cells, and antiangiogenesis. Cytotoxicity of snake venoms is related to alterations in cellular metabolism with a major effect on tumor cells when compared with normal cells[3-5].

3. Conclusions

Venoms of *Bothrops newweidii*, Indian cobra *Naja Naja*, *Naja nigricollis*, *Naja naja atra*, *Bothrops Leucurus*, *Opiophagus Hannah*, *Bothrops jararacussu*, *Naja Kaouthia*, *Okinawa Habu*, *Lapemis curtus*, *Daboia russelli russelli, Walterinessia aegyptia, Crotalus durissus terrificus, Agkistrodon acutus, Macrovipera lebentina, Bungarus multicinctus, Bungarus fasciatus, Laticauda semifasciata and Agkistrodon rhodostoma* are of potential use in research directed towards management of cancer[1-6].

Tagging gold nanoparticles with snake venom components has been found to increase their uptake by tumor cells[11]. Also silica nanoparticles tagged with snake venom components are observed to act specifically on tumor cells without affecting normal cells[12]. Novel snake venom delivery system with clinical applications to suppress tumors such as intravenous liposomal delivery, recombinant adenovirus carrying snake venom cystatin gene has been described in the literature[6]. Innovative research is required to discover novel, effective therapeutic anticancer agents from snake venoms in oral cancer patients. This promising area of research may bring hope, smile, comfort and cure to these group of cancer patients.

Conflict of interest statement

We declare that we have no conflict of interest.

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