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RESEARCH ARTICLE

An overview on snake venom anti-cancer activity

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Abstract:
Snake venom instead of causing mortality and morbidity in human, is also therapeutically very crucial in treating various forms of cancer such as, prostate cancer, ovarian cancer, breast cancer, leukemia etc. Different types of snake have different types of venom, inducing apoptosis, cytotoxicity, anti-proliferative activity, activating platelets by targeting platelet CLEC-2 and inhibiting the production of DNA and RNA. This review focuses on different types of snake venom having anti-cancer property.

Key Words:Venom, Leukemia, Cancer

Introduction

Cancer is a multi-factorial disease mostly occurred due to uncontrolled production of cells, local tissue attack and their ability to metastasize. Two factor are involved which can caused cancer. These factors include external factors such as, radiations, chemicals, tobacco, viruses etc. Internal factors which involves, immune conditions, hormones, and mutations. This may act together or in sequence to instigate or promote carcinogenesis. Cancer is the third leading source of death in the world after heart and infectious diseases [1,2]. It was reported in 2008 that cancer was responsible for 7.6 million deaths worldwide, mostly in the economically developing countries, and its numbers is constantly growing due to aging, growth of the world's population and cancer-causing behaviors [3].Cancer is important public health problem worldwide because, it has a high mortality and morbidity worldwide; there is an urgent need to find better treatment. Treatment modalities towards the cancer comprise surgery, radiation therapy, hormonaltherapy, chemotherapy, and immunotherapy [4]. Chemotherapy remains the predominant option [5]. Chemotherapeutics used in systemic administration often lead to serious side effects [6]. This has led to the development of new strategies to achieve effectiveness against cancer. In this sense, novel anticancer drugs developed fromnatural resources may increase the efficacy of conventional chemotherapeutic drugs[7].Biotoxins are produced by living organisms which can kill or hurt other organisms. They have both toxicological effect and pharmacological effect, which contain abundant natural sources of novel compounds that may serve as a starting material for drug design to combat several pathophysiological problems such as cancer and may have applications in cancer therapy. At present, many active principles produced by biotoxins have been employed in the development of new drugs to treat diseases such as cancer[8].Many toxins of venomous species present great potential as anti-tumor agents, such as snake venom is a unique source from which novel therapeutics can be developed. Snake venoms toxins contributed significantly to the treatment of cancer [9].

Snake

Snakes have been a subject of fascination,terror and mythsall over the past. In earlyEgypt the cobra was worshipped and its imitation was used to beautify the crowns of Roman emperors. In the olden Greek world, the god of medicine was depicting with a stick entwined with a snake.Thesymbol that is still usedto represents the guilds of pharmacy and medicine. About 2.5 million people around the world are the victims to snake bites annually, about 100,000 lose their lives. The majoritymortality and morbidity occurs in rural areas in the tropics [10,11].

Snake is the most shining familiar venomous land animals. Which have significantly developed glands to produce venom with different apparatuses todeliver the venom into the prey. The composition and biological activities of snake venoms differ based on the family,genus and species of snakes additionally their environments, diets and sex [12,13].

There are about more than 200 species of venomous snakes found on the earth, classified into four major families: Hydrophiae, Elapidae,Viperidae, and Crotalidae. They have a venom gland that synthesizes, stores and secrete about50-60 protein/peptide components with different functions and structures, as either theinactive or active precursor form, into the site of their bite.The precursor forms of components are activated by a special mechanism after the secretion. The venom components seem to be moderately common and similar with one another within each family of snakes but they are basically different depending on each snake species [14,15].

Composition of Snake venoms

Snake venomsare produced in venom glands throughout life of the snake which is collected with scientific approaches and techniques [16]. Different species of snake have different types of venom depending upon its location, age, habitat, etc. The concentration of secreted venom from glands depends upon the climate and season [17].Snake venom produces toxicity when it is injected into the blood but, harmless when it is ingested. It is a transparent and viscous liquid, which can be dried in the form of crystals[18].Snake venoms are secreted by venom glands, a mixture of enzyme,proteinaceouspeptidyl toxins and small organic substances, for example citrate, nucleosides and acetylcholine. [19,20,21]. Snake venoms also contain inorganic cations (Ca, K, Mg, Na etc.), lipids, carbohydrates, and free amino acids[22]. Snake venom also has a numeral bioactive substance and a natural source of a variety of compound including neurotoxic, cardiotoxic, cytotoxic and many additional active compounds [23].

Classification of snake venom

According to effect and mode of action, Snake venoms areclassified into three groups,neurotoxin, hemotoxinand cytotoxin [24]. Neurotoxins target central nervous system causing heart failure and breathing problems. They have the ability to inhibit ions movement across the cell membrane and block the communication between neurons[25]. Hemotoxins are the toxins that cause destruction of RBC. It affects cardiovascular system and blood functions. It also targets the muscle tissue of the host. Cytotoxic venoms target specific cellular sites or muscles. Cobra, Kraits, Sea snakes contain neurotoxic venom whereas Rattle snake and Copper heads have hemotoxic venoms. Snake bite results in subcutaneous injection of venom into the prey which results in local and systemic effects. The local effects include hemorrhage and dermonecrosis. Systemic toxicity includes myo-toxicity, anticoagulant activities and hypotensive [26,27].

Mechanism of action

Venom of snake toxins causes fibrinolytic activityin patients. It contains enzymes that very quickly clot fibrinogen andimpose strong lethal effects. Snake venom enzymes eliminate fibrinogen fromthe circulation with no converting it to fibrin and responsible for heavy platelet aggregation.A strong fibrinolytic activity in snake venoms is generated by enzymefibrogenase (*Viperalebatina*), Natrahagin proteinase (*Najanaja*) fibrolase (*Agkistrodoncontortrix*),atroxase (*Crotalusatroz*), and lebetase from (*Viperalebetina*) which inhibit platelet aggregation. Similar finbrinolytic activity isshown by Batraxin and Hannahpep[28,29]. Venom proteinases such as thrombin proteinases, plasminogen activator proteinases and fibrinolyticproteinases cleave peptide bounds present in fibrinogen. Snake venom causes peripheral atrial thrombosis and deep vein, also the reason for cerebral and myocardial infarction, priapism and sickle cell crisis. Great interestingly, venom toxins show antitumor activity due to release of H2O2 in oxygen dependent enzymatic reactions and inflammatory responses mediated by IL8 and IL2, TNF-α and other soluble factors [30].

Snake venoms as anticancer agent

Claude Bernard recognized for the first time that the physiologically active components of snake venom may contain therapeutic potentials. Calmette reported the use of venom for the treatment of cancer in laboratory animal for first time [31].Venom extracted from *Walterinnesiaaegyptia*(WEV) alone or in combination with silica nanoparticles (WEV+NP) used for the treatment of prostate cancer cells. Venom toxins isolated from *Viperalebentinaturnica* induces apoptosis of ovarian cancer cells [32].Salmosin is a disintegrin purified form of venom obtained from Korean snake, interacts with integrin and induces apoptotic cell death by competing with the extracellular matrix for direct binding to integrin on the cell surface [33]. Aggretin is another snake venom-derived protein which activates platelets by targeting platelet CLEC-2 so as exerting anti-tumor metastatic effects [34].*C.*

*albolabris*and *C. rhodostoma*venoms have similar cytotoxic effects on KATO-III, BT474, SW620, Cha GO and Hep-G2 cancer cells and both venoms showed superior potency on KATO-III and BT474 cells as compare to anti-cancer drug [35]. Crude venom of Cobra snake considerably decreases the production of DNA and RNA in breast cancer [36].Egyptian cobra (*najahaje*) venoms also show potent activity for prostate and breast cancer cell lines [37,38]. PLA2 isolated from *Bothropsnewweildii*venom shows cytotoxic activity in melanoma [39].Morespecially, *Bothropsjaroraca*and *Crotalusdurissusterrificus*caused cytotoxicity in sarcoma and leukemic tissues [40].Snake venom mainly from members of family elapidae, viperaidae and crotalidae kill melanoma and sarcoma cells and showed growth inhibitory activity and cytotoxicity in chodrosarcoma cell lines [41]. Disintigrin andsaxatilin isolated from Korean snake venom,*Gloydiussaxatilis*inhibit the proliferation of ovarian cancer cells[42].Crude cobra snake venom at the rate of 25 µg / ml reduces nucleic acids production in humanbreast cancerous tissue *invitro*. It suggests an ideal model for examining the anticancer activityand could be a better substitute in comparison to presently available anti-tumor drugs fortherapeutic use in breast cancer in future [43]. Venom isolated from *Najanajaatra*cardiotoxins inhibit the growth of K562 cells and exhibit apoptosis in cancer cells. *Crotalusdurissusterrificus*and *Bothropsjaroraca*showed cytotoxicity in sarcoma and leukemic tissues [44]. Venom extracted from *Walterinnesiaaegyptia* (WEV) either alone or in combination with silica nanoparticles (WEV+NP) mediated the growth arrest and apoptosis of breast cancer cells or prostate cancer cells [45]. A silica nanoparticle-based snake venom delivery model targets cancer cells, but not normal cells, has been studied. Results show that when the snake venom extracted from *Walterinnesiaaegyptia* (WEV) was combined with silica nanoparticles (WEV+NP), it strongly enhance the antitumor activity in two breast carcinoma cell lines [46]. Contortrostatin (CN) (Mr 13,500) is a homodimericdisintegrin, isolated from the Southern Copperhead snake venom. Antitumor activity of CN is primarily modulated by its high-affinity interaction with several integrins displayed on both cancer cells and newly growing vascular endothelial cells. These diverse mechanisms of action provide CN a clear advantage over other antitumor. Swenson *et al.* extends and improves above studies by describing a clinically relevant delivery system for this highly effective antitumor agent-i.v. delivered liposomal CN (LCN), which passively accumulates at the tumor site where it not only limits tumor growth and angiogenesis but also severely curtails tumor metastasis [47-48]. Studies have shown that transfection of the snake venom cystatin (sv-cystatin) gene can inhibit the invasion and metastasis of tumor cells and adenovirus carrying sv-cystatin (Ad/sv-cystatin), indicating that Ad/sv-cystatin suppresses mouse melanoma invasion, metastasis, and growth in vitro [48] .Disintegrins are a family of small proteins (45-84 amino acids in length), many of which are found in snake venom that function as potent inhibitors of both platelet aggregation and integrin-dependent cell adhesion [48].

Conclusion

Snake venoms are therapeutically very important target against various forms of cancer. As there are hundreds types of snake and each type of snake have different composition of venom. Further studies are needed to investigate the anti-cancer property of other snake commonly found in our localities.

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