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Review Article

Venom proteins; Prospects for anticancer therapy

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Abstract:

Cancer is a very special disease identified by very rapid growth of modified cells. Due to uncontrolled spread of cell, it may be resulted in death. They hold the second main reason of mortality, cardiovascular diseases being first, in developed countries and stand at third after infectious and cardiovascular diseases in developing countries. Several millions new cancer-patients are being diagnosed worldwide each year resulting in many deaths. Several natural products have been the pillars of chemotherapy of cancer for the last 40 years. But majority of the recently designed anticancer agents cause unfavorable adverse effects due to lack of tumor specificity and multidrug resistance. So, the search for effective, safe and selective anticancer drugs is vital for new drug designing in the field of research of cancer. As the natural products show a diverse range of structure, they become more efficient templates for the designing of new compounds. Venom protein may act as a potent anticancer agent against several types of cancers. Out of a vast variety of venom proteins, snake venom, bee venom, wasp venom and scorpion venom have potential effects as an anticancer therapy.

Key words: cancer cell; anticancer activity; snake venom; apoptosis;

Introduction:

Cancer is the large class of disorder characterized by quickened and abnormal growth of variant cell which have no ability of apoptosis [1]. Cancer is non-stop degenerative infection. In economically developed countries majority of death are caused by cancer and cancer is thought to be the second common death leading disorder in those countries [2, 3]. For treatment of cancer different types of approaches such as radiation, surgery therapy, chemotherapy and immunotherapy are utilized. These approaches are still in used, separately or in grouped [4].

Basically cancer is a disease of tissue growth regulation. When the genes which are responsible to regulate cell growth and differentiation, become altered, normal cell is transformed into a cancer cell. Generally, modifications in number of genes are responsible to change a normal cell into a cancer cell. There are 2 main types of genes which are affected by these changes i.e. oncogenes which may be normal genes whose expression is elevated to an abnormal level, or altered genes which have specific characteristics. In each case, expression of these genes elevate the virulent phenotype of cancer cells.

Cancer is initiated by many reasons including external resources (tobacco, chemicals, radiation and infectious organisms) and internal causes (inherited mutations, hormones, immune conditions and mutations due to metabolism).

The tamoxifen was the 1st FDA approved chemopreventive drug for limiting the risk of breast cancer up to 50% in women having high risk. Utilization of tamoxifen resulted in multiple adverse effects such as uterine cancer, blood clots, ocular disturbances, hypercalcemia, and stroke. Due to these adverse effects of the chemopreventive drugs, serious issues are raised in case of administration of a drug to healthy people for prevention of cancer for a long period. Therefore the more safe and potent drugs are needed for preventing cancer. So the natural components derived from natural resources are the most efficient for this purpose.

Recent report of International Agency for Research on Cancer (IARC) estimated that the new cases of cancer are rise 10 million per year. According to the estimation of WHO, cancer is a disorder by which about 13.1 million deaths will cases in 2030 [5]. For cancer therapy new anticancer drug are searched which is the goals of biotechnological research. A number of compound such as venom of several animals and plants including snake, scorpion's wasp, bee and cnidarians etc are mostly exposed for treatment of cancer because those have pharmacological and biotechnological usage [6-7].

Anticancer activity of snake venom:

Snake venom are the emission of venomous snakes that are produced and accumulate in definite part of their body like that venom gland. Snake venom are compound mixture; mostly proteins, carbohydrate, enzymes, lipid and inorganic cations. About 90-95 % snake venom are formed by protein and peptide. Inorganic cations include Calcium, Magnesium, Sodium and potassium are also present. It also contain little amount of Zinc, Cobalt, Magnesium, Iron and Nickel [8]. L-

amino acid oxidases, Phospholipases A, mettalloproteases and serineproteases are enzyme present inside the snake venom [9]. About 25 enzyme are present in snake venom but these all are not present in a single venom. Snake venom contain maximum toxicity due to that compose them a selective expansion of anticancer agent [10].

Snake venom are utilized in the cure of cancer, inflammatory disorder, pain, thrombosis and blood disease [10-11].

Snake venom L-amino acid oxidases (LAAO):

Living organism for example Snake, microbes, fungi and algae have enzyme which diffusely dispersed in their body. LAAOs are additionally found in venoms of a few snake animal varieties [12]. Rodrigues et al. purify and demonstrate that Borthrop pauloensis are snake venom that contains Bp-LAAO, an L-amino oxidase which is use as an anticancer agent as well as bactericidal, dose-dependent leishmanicidal activity. The anti-cancer activity of LAAO are seen in the cancer cells of breast in human (SKBR-3), Ehrlich ascetic tumor line of the cell (EAT) and leukemia T cell (JURKAT) [13]. Agkistrodon acutus venom also contain LAAO which demonstrated that in cell cycle sub –G1 phase of tumor aggregation take place. It likewise initiated apoptosis in human alveolar epithelial cell line through pathway known as Fas in the cells A549 (HAECL) [14, 15, and 16].

Snake venom Phospholipases A:

Various kinds of phospholipases expose to have the properties of angiogenesis i-e basic and acidic PLAs [17-18]. Lately, CC-PLA-1 &CC-PLA-2 are two phospholipases A derived from Cerates. Cerates venom were characterize and decontaminated. In vivo and vitro CC-PLA-1 &CC-PLA-2 have the ability to stop the attachment and movement of cancer cell, directed by angiogenesis [19, 20]. Viperidae venom contain certain PLAs which have anticancer activity. Significance of these PLAs is that it deliver the new class of anticancer agent which play important role in new molecular & biological perception in the development of drug for cancer [13,20].

Disintegrins:

Disintegrins have low molecular weight about (5 to 10 KDa). It is large class of nonenzymatic, RGD-containing peptide and nontoxic which naturally occurring in the venom of snake. Initially,

those compound have capability to act together by αIIß3, αIIbß3 & αvß3IIs integrins that are shown through numerous cell which concerned in cancer growth and production.[21-22].

Disintegrin consist of Arg-Gly-Asp are contortrostatin (SN) that separated from Venom of Agkistrodon contorix. These compound attached with various receptors of endothelial cell surface &epithelial carcinoma. Contortrostatatin (CN) is a 13.5kDa protein that act as anticancer. Schmimtmeier et.al establish that CN identify αIIβ3, α5β5 and α5β3 integrins[23].

Anticancer activity of bee venom:

Bee venom are distinctive armament material in kingdom animalea. Bee venom are isolated from the venom gland that found in the abdominal cavity. Bee venom consist of many peptides such as melittin, adolapin and apamin; enzyme such as phospholipase A2 (PLA, peptide like that dopamine, norepinephrine and histamine [24-25]. Melittin are found in Apis mellifera honeybee contains 26 amino acid [26]. These are used in diverse membrane perturbing properties i-e anticancer & hemolytic activity [27]. In vivo carcinoma cells production and growth of cancer are prevented by bee venom. Prevention of cancer growth lead to stimulate the response of cellular immune within lymph node [28,29].

Now a days, several study described that growth of cancer cell are inhibited by certain natural occurring products.The significance of these natural products are to cause cell death act as a medicine used for human cancer treatment [30]. In the earlier two eras, bee venom consist of peptides called melitten. The Melilten is a large protein component, involve in the therapy of cancer [28, 31, 29, 32, 33]. Arthropod produce venom, mostly bee venom are studied due to their uses in anti-tumor activity, melittin and PLA2 are two components that are separated from bee venom. Several publication described that venom PLA2&Melittin found in the Apis mellifera ,a species of bee that are used in the effect of anti-cancer [34].

Melittin (A bee venom protein):

Melittin are the major toxin isolated from the venom of Apis mellifera, a species of bee and existence of compounds of molecules which comprising a group of polar water soluble compounds that attached to a water with insoluble chain of hydrocarbon. It is small peptide and consist of 26 amino acid residue [35]. Melittin are involved in many cancer cell treatment such as breast cancer, lung cancer, leukemia and renal. All these are mark by Melittin [36]. Now a days, a studies

described that by causing many mechanism of cell death, melittin destroy the cancer cell through apoptosis. These mechanism involved inactivation of MMP and caspase [37, 38]. The effect of melittin and melittin –conjugate hormone receptor for example Hecate are exposed to partake in anticancer activity in the tumor of testes and ovaries. Gawronska described that expression in tumor tissue and OVCAR -3 cell contaning the hCG receptor protein and luteinizing hormone [39].

Recently, studies reported that melittin show the anti-cancer activity by utilizing nanocarrier to transport the melittin to the cancer cells. Advanced in nanotechnology and biotechnology novel technique are used that lead to advance in cure of cancer cell e.g. the gene that code the melittin are transported through vector by using transfection process [40].

Anticancer activity of Wasp venom:

Wasp comprises a complicated gland which is liable for the injection and production of the venom. Due to biochemical, pharmacological and physiological accomplishments, this venom perform a key role in diverse mechanisms of survival such as to defend in contradiction of pray captures and predators [41, 42 .43, 44]. Besides causing serious problems of the health, focused studies on the compounds which are bioactive present in the venom of wasp, such as proteins, peptides and amines of biogenic [45].

These bioactive compounds have anti-cancer potential. Among them, mostly the mastoparan molecule is studied, a peptide of amphipathic with 14-amino acid chain and it has been reported that mastoparan by forming a permeability pore, make an effective permeability in the mitochondrial transition with the intensity of variety between 5 µM and 100 µM [46]. Due to its capability for making permeability of mitochondria and specific deficiency for the cells of tumor [47] for delivery selective to mitochondria in the cells K562 chronic leukemia of myelogenous in human. This molecule is en-capsulated through liposome modified transferrin- with sensitive pH to GALA (peptide of fusogenic). With a high expression of transferring receptors this liposome targets the cells and get internalized through these receptors by endocytosis. Finally encapsulated mastoparan was demonstrated its anti-cancerous significant through cytochrome C transferring in the line of the cell studied.

From social wasp venom through paulista of Polybia, Souza et al., isolated 2 novel peptides of mastoparan, Polybia-MP-III and Polybia-MP-II, which revealed hemolytic action proceeding to

erythrocytes [48]. Wang et al. studied that MPI-Polybia was shown to have the activity of anti-tumor [49]. MPI-Polybia has ability to target nonpolar cell of lipid membrane, form permeable ion channels which leads to depolarization, cytolysis which is irreversible and causes death of the cell, because of antibiotic activity of Polybia-MPI peptides [50]. As compared to normal cells, the cells of tumors are nearly fifty times additional susceptible to peptides of lytic. It more ever exposed that in non-tumorigenic cell line NIH3T3 the proliferation was relatively unaffected, whereas by the mechanism of membrane disrupting the cells of the tumor and endothelial associated cells can significantly inhibit by Polybia-MPI peptide. The anti-tumor activity of Polybia-MPI enhanced, as its acts on cells of endothelial proliferating and cells of the tumor.

For the 1st time, the arrangement of a molecule that is anti-cancerous were remote from the external wrapping simillima of the societal wasp Vespa and determined by Fujiwara et al. [51]. This 7 and 8 SPF (para-seco -ferruginone), a biologically active quinone shows an effect at the inhibition of the growth on cancer cells in the liver of rat. The writers recommend that particular cells exposed to this molecule brings changes with in morphological that encourage apoptosis through cytotoxic activity.

Anticancer activity of Scorpion venom

Scorpion venom consist of a mixture of small molecules, peptide, protein and salt. Against ANTP (Peptide of tumor) sub-atomic with 6280 Da of mass was cleaned by filtration chromatography through gel and HPLC, from the venom of Buthus martensii Karsch that counteracted multiplication of the S-180 mouse cells of fibrosarcoma and murine cells EAC [52]. CTX (Charybdotoxin), a neurotoxin of 37 amino acid of the venom from the scorpion Leiurus quinquestriatus hebraeus, prompted impasse via Ca^{2+}-enacted channels of K^{+}, produced a small depolarization into the tumor cells of breast in human and successively captured the G1early cell, G1 of late, and stages S and cells gathered in the stage S [53]. Bengalin, a high sub-atomic weight protein confined from the Indian black scorpion (Heterometrus bengalensis) venom indicated anticancer activity, on U937 and K562 cell. Bengalin inspired loss of mitochondrial film potential which started cytochrome c discharge in cytosol, diminished warmth stun protein (HSP) 70 and 90 expression. This demonstrated, bengalin may give a reputed atomic component to their anticancer impact in cells leukemic of human which may be interceded by mitochondrial passing course [54].

Conflict of interest: On behalf of all authors, the corresponding author declare that there is no conflict of interest.

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