MINI-REVIEW

Biotoxins for Cancer Therapy

Cui-Cui Liu*, Hao Yang, Ling-Ling Zhang, Qian Zhang, Bo Chen, Yi Wang

Abstract

In recent times, a number of studies have provided evidence that biotoxins present great potential as antitumor agents, such as snake venom, bee venom, some bacteria toxins and plant toxins, and thus could be used as chemotherapeutic agents against tumors. The biodiversity of venoms and toxins make them a unique source from which novel anticancer agent may be developed. Biotoxins, also known as natural toxins, include toxic substances produced by plants, animals and microorganisms. Here, we systematically list representative biological toxins that have antitumor properties, involving animal toxins, plant toxins, mycotoxins as well as bacterial toxins. In this review, we summarize the current knowledge involving biotoxins and the active compounds that have anti-cancer activity to induce cytotoxic, antitumor, immunomodulatory, and apoptotic effects in different tumor cells *in vivo* or *in vitro*. We also show insights into the molecular and functional evolution of biotoxins.

Keywords: Biotoxins - venoms - toxins - cancer

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Introduction

Cancer has emerged as an important public health problem worldwide. Since it has a high morbidity and mortality worldwide, there is an urgent need to find better treatment. Treatment modalities towards the cancer comprise radiation therapy, surgery, chemotherapy, immunotherapy and hormonal therapy (Baskar et al., 2012). Out of the therapies being used for treatment, chemotherapy remains the predominant option. However, patients often develop resistance to chemotherapeutics acquired by tumors (Lai et al., 2012). In addition, chemotherapeutics used in systemic administration often lead to serious side effects (Soletti et al., 2008). This has led to the development of new strategies to achieve effectiveness against cancer. In this sense, novel anticancer drugs developed from natural resources may increase the efficacy of conventional chemotherapeutic drugs (Libério et al., 2013). At present, many researchers around the world have found compounds that are often poisonous reveal anticancer property.

Biotoxins are produced by living organisms which can kill or hurt other organisms. They have both toxicology 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 (Heinen and da Veiga, 2011). The difference of structure and composition of biotoxins provide valuable ideas for the research of the antitumor drugs. Studies have found evidence that many toxins of venomous species present great potential as anti-tumor agents, such as snake venom, bee venom, some bacteria toxins and plant toxins (Grant et al., 2004).

Venom is secretion of organisms, which are synthesized in venom gland. Natural venoms are useful biological resource, containing several pharmacologically active components that could be of potential therapeutic value. Many biotoxins have antitumor activity, some of them killing tumor cells directly, some inhibiting tumor angiogenesis and inhibiting tumor growth (Orsolic, 2012; Jain and Kumar, 2012). Here are several representative biological toxins that have antitumor applications.

Antitumor activity of snake venom

Snake venom is a complex mixture of pharmacologically active substance. Proteins and peptides accounted for approximately 90-95% of venom's dry weight (White, 2005). These proteins may be toxic or non-toxic. In vivo and in vitro experiments showed that snake venom has inhibitory effect on tumor, and may have applications in cancer therapy. Use of venom for the treatment of cancer in laboratory animal was first reported by Calmette, 1993. It was found that snake venom toxins from Vipera lebentina turnica induced apoptosis of ovarian cancer cells. Venom extracted from Walterinnesia aegyptia (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 (Badr et al., 2013). A silica nanoparticle-based snake venom delivery model that targets cancer cells, but not normal cells, has been studied. Results show that when the snake venom extracted from

*Department of Scientific Research, Hong Hui Hospital, Xi'an Jiaotong University College of Medicine, Xi'an, China *For correspondence: cliu_honghui@126.com*

Walterinnesia aegyptia (WEV) was combined with silica nanoparticles (WEV+NP), it will strongly enhance the antitumor activity in two breast carcinoma cell lines (Al-Sadoon et al., 2013).

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 (Jakubowski et al., 2013; Lucena et al., 2014). Salmosin is a disintegrin purified from venom of a 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 (Hong et al., 2003). Contortrostatin (CN) (Mr 13,500) is a homodimeric disintegrin 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 impoves 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 (Swenson et al., 2004).

Studies have shown that transfection of the snake venom cystatin (sv-cystatin) gene can inhibit the invasion and metastasis of tumor cells, so Xie et al. constructed a recombinant adenovirus carrying sv-cystatin (Ad/sv-cystatin) indicate that Ad/sv-cystatin suppresses mouse melanoma invasion, metastasis, and growth in vitro and in vivo (Xie et al., 2013). Son et al. have found the anticancer efficacy of SVT and mechanistic rationale (cell cycle arrest and apoptosis induction) against advanced human prostate cancer cells in extremely low concentrations (in vitro ; below 2 μg/mL, in vivo ; 0.4 mg/kg, in vivo) and could be useful as a novel agent for human prostate cancer prevention and/or intervention. Studies in in vivo animal experiment further suggest that SVT significantly inhibited tumor growth by ~40% to 50%, but did not induce any serious health problems. Therefore SVT could be safely used in a therapeutic application (Son et al., 2007).

Cathelicidin-BF (BF-30) is a natural antibacterial peptide extracted from snake venom toxins from Bungarus fasciatus. It's composed of 30 amino acids. Wang et al. has studied the anticancer activity of BF-30 on the proliferation of the metastatic melanoma cell line B16F10 in vitro and in vivo. BF-30 is supposed to possess anti-proliferative, anti-migratory and anti-angiogenic property (Wang et al., 2013). Aggretin is another snake venom-derived protein which activates platelets by targeting platelet CLEC-2 so as exerting anti-tumour metastatic effects (Chang et al., 2014).

Antitumor activity of bee venom

Bee venom is used to treat various diseases in oriental medicine, including arthritis, rheumatism, tumor and skin diseases (Hider, 1988). It contains at least 18 kinds of active compounds, including melittin (a major component of BV), apamin, adolapin, the mast-cell-degranulating (MCD) peptide, enzymes (phospholipase A2, and hyaluronidase) as well as non-peptide components, such as histamine, dopamine, and norepinephrine which have a variety of pharmaceutical properties (Son et al., 2007). Recent studies reported several effects of bee venom such as induction of apoptosis and necrosis and effects on proliferation, cytotoxicity, and growth inhibition of different types of cancer cells, including prostate cancer (Park et al., 2011), breast cancer (Ip et al., 2008), ovarian cancer (Jo et al., 2012), lung cancer (Huh et al., 2010), liver cancer (Liu et al., 2008), bladder cancer (Ip et al., 2012) as well as leukemia (Moon et al., 2006). BV induces apoptotic cell death through several cancer cell death mechanisms, among them the activation of PLA2 by melittin is the critical mechanism for the anti-cancer activity of BV. The conjugation of cell lytic peptide (melittin) with hormone receptors and gene therapy carrying melittin can be useful as a novel targeted therapy for some types of cancer (Orsolic, 2012; Kollipara et al., 2014).

Melittin, present in bee venom about 50–70%, is an antimicrobial peptid of bee venom. Park et al. indicated that bee venom and melittin could inhibit prostate cancer in in vitro and in vivo through activation of caspase pathway via inactivation of NF-κB (Park et al., 2011). It has also reported that BV induces apoptosis in Human Breast Cancer MCF7 Cells either by caspase-9 and-3 activation or through the release of EndoG and AIF from mitochondria (Ip et al., 2008). Also, Jo et al. found that bee venom and melittin induce apoptotic cell death in ovarian cancer cells through enhancement of DR3, DR4, and DR6 expression and inhibition of JAK2/STAT3 pathway (Jo et al., 2012). Authors also concluded that BV takes effect by blocking the tyrosine phosphorylation of VEGFR-2 so as exerting anti-angiogenic activity, and validate the application of BV in lung cancer treatment (Huh et al., 2010). A recent study by Liu et al. found that melittin derived from the venom of the bee inhibits cell motility drastically and prevents HCC metastasis via inhibition of Rac1 (Liu et al., 2008). Ip et al. found that BV-induced apoptosis occurs through multiple pathways in human bladder cancer TSGH-8301 cells by inducing the release of reactive oxygen species and Ca2+and ER stress-mediated apoptotic death, and promoting the activation of initiator caspases and effector caspase with adaptor proteins (Fas/CD95) act as a receptor for BV (Ip et al., 2012). Observations by Moon et al. report that BV induces apoptosis in leukemic U937 cells through down regulation of ERK and Akt signal pathway with Bcl-2 and caspase-3 as key regulators in BV-induced apoptosis (Moon et al., 2006). Above in vitro and in vivo trials have demonstrated that BV therapy may be an important modality to treat different types of cancer.

Antitumor activity of other animal toxins

There are other animal venoms possess therapeutic potentials, such as scorpion venom, sea anemone toxin. Studies show that the different constituents of scorpion venom can modulate cell proliferation and cell

growth. The cytotoxic activity of Indian black scorpion (Heterometrus bengalensis Koch) venom was explored on human leukemic U937 and K562 cells. The scorpion venom showed characteristic features of antiproliferative, cytotoxic and apoptogenic activity against human leukemic cells (Das Gupta et al., 2007). In Cuba the endemic species of scorpion Rhopalurus junceus have been used in traditional medicine for cancer treatment. Diaz-Garcia et al. concluded the scorpion venom from R. junceus possessed a selective and differential toxicity against epithelial cancer cells which could be a promise natural product for cancer treatment (Díaz-García et al., 2013).

Soricidin, a 54-amino acid peptide, isolated from the paralytic venom of the northern short-tailed shrew (Blarina brevicauda) and has been found to inhibit the transient receptor potential of vallinoid type 6 (TRPV6) calcium channels that are up-regulated in a number of cancers (Stewart et al., 2009). Studies suggest that SOR-C13 and SOR-C27, two shorter peptides, derived from the C-terminus of soricidin, may provide an avenue for the early detection and treatment of TRPV6-rich tumors and have potential applications for a range of carcinomas including ovarian, breast, thyroid, prostate and colon, as well as certain leukemia's and lymphomas due to there high-affinity antagonists of human TRPV6 channels (Bowen et al., 2013). Also, Bufalin, obtained from the skin and parotid venom glands of toads, has been demonstrated to induce apoptosis in some lines of human tumor cells, such as endometrial and ovarian cancers (Takai et al., 2012). Huang et al. reported that Cinobufacini, an aqueous extract from the skins of Bufo bufo gargarizans Cantor, could not only increase the anti-tumor effect of cisplatin but also suppress the side effects of chemotherapy, which might be related to up-regulation of Fas expression (Huang et al., 2012). Furthermore, studies found that sea nettle nematocyst venom (SNV) peptide possessed significant antitumor effect on Ehrlich ascites carcinoma (EAC) tumor (Balamurugan et al., 2010). Four isoforms of actinoporin (RTX-A), isolated from the tropical sea anemone Heteractis crispa (=Radianthus macrodactylus), demonstrated potential cancer-preventive activity at extremely low and non-cytotoxic concentrations through the induction of p53-independent apoptosis and inhibition of the oncogenic AP-1 and NF-κB nuclear factors activity (Fedorov et al., 2010).

Antitumor activity of plant toxin

Phytochemicals have provided an abundant and effective source of therapeutics for the treatment of cancer. However, compared with animal toxins, the antitumor researches of plant toxin are much less. Gnidimacrin is a diterpene compound found in the methanol extract of Stellera chamaejasme L, showed significant antitumor activities against mouse leukemia P-388 and L-1210 in vivo (Feng et al., 1995). Accordingly, two biflavonones: chamaejasmenin B and neochamaejasmin C, isolated from the root of Stellera chamaejasme L (known as the traditional Chinese herb Rui Xiang Lang Du) is recommended for cancer therapy. The two compounds are potential anti-proliferative agents in 8 human solid tumor cell lines: Human liver carcinoma cell lines (HepG2 and SMMC-7721), a human non-small cell lung cancer cell line (A549), human osteosarcoma cell lines (MG63, U2OS, and KHOS), a human colon cancer cell line (HCT-116) and a human cervical cancer cell line (HeLa). Furthermore, they induce cell cycle arrest, apoptosis and DNA damage (Zhang et al., 2013). In addition, persin, previously identified from avocado leaves as the toxic principle responsible, induces Bim-dependent apoptosis in human breast cancer cells, and could represent a novel class of microtubule-targeting agent with potential specificity for breast cancers (Butt et al., 2006).

Some plant toxins are applied in cancer immunotherapy, including in vitro and in vivo pre-clinical studies and clinical trials. Saporin-S6 (also known as saporin), first isolated from Saponaria officinalis L. seeds, is widely employed in the construction of conjugates and immunotoxins for different purposes. The immunotoxin has shown high enzymatic activity, stability and resistance to conjugation procedures and blood proteases when used in cancer therapy, particularly in hematological tumors, which make saporin-S6 a very useful tool in cancer therapy (Polito et al., 2013). Ricin toxin (RTB) from castor plant is used as a vaccine adjuvant/carrier to design cancer vaccines, since it has the most effective immunogens. The research of Sadraeian et al. verifies the clinical applications and the future prospects for development of HPV-16 E7 therapeutic vaccines in fusion with ricin B chain against cervical cancer (Sadraeian et al., 2013).

Antitumor activity of mycotoxins

Mushrooms have been used as traditional medicines since ancient times, and the results of recent studies have elucidated the anticancer actions of various mushroom components, including poisonous varieties.

MGI 114 (6-hydroxymethylacylfulvene, HMAF) is a novel semisynthetic antitumor agent derived from the sesquiterpene mushroom toxin illudin S. Although illudins did not demonstrate significant activity as antiproliferative agents in tumor-bearing animals, several properties including its potent inhibition of DNA synthesis and a unique interaction with DNA led to a structure-activity-based synthetic effort to obtain analogs with improved therapeutic potential. These results demonstrate that MGI 114 exhibits a broad spectrum of antitumor activity against both adult and pediatric primary tumor colony-forming units in a concentration-dependent manner both at short and prolonged exposure duration. The substantial in vitro activity of MGI 114 at concentrations achievable in clinical trials, together with its activity against tumors resistant to classic standard cytotoxic drugs, justifies the further clinical evaluation of this unique agent (MacDonald et al., 1997; Hidalgo et al., 1999).

In the molecular sense, A. phalloides has been newly discovered to have activity as an inhibitor specific for tumor cells. The immune system might recognize and lyse tumor cells, and partial inhibition of tumor cell activity raises the possibility for stabilization of the disease. Amanita treatment already showed good results in

prophylaxis or cure of a number of tumor cases. To expand the possibilities of experimental medicine, a pilot study of treatment of B-cell chronic lymphatic leukemia (B-CLL) showed that homeopathic dilutions from A. phalloides offer a strong tool for the therapy of cancer (Riede, 2010).

Agaricus blazei Murrill, a native mushroom of Brazil, has been reported to be an immunoreactant with anti-tumor effect. Thus, Kobayashi, H. and J. Masumoto found that an inhibitory effect on the growth of sarcoma 180 implants in vivo was induced by peritoneal injection of a freeze-dried, hot water extract of Agaricus blazei Murrill (FAG). Hence, the contaminated endotoxin of Agaricus blazei Murrill may act as an immunomodulator of anti-tumor activity (Kobayashi and Masumoto, 2010).

Antitumor activity of bacterial toxins

Many bacterias also play an important role in the development of potent therapeutic agents. Shiga toxin 1 (Stx1), produced by some pathogenic escherichia coli strains (Engedal et al., 2011), targets a restricted subset of normal and cancer human cells expressing globotriaosylceramide (Gb3Cer/CD77) on their membrane. In spite of the high toxicity (Sandvig, 2001), stx1 has been proposed in the treatment of Gb3Cer/CD77-expressing lymphoma. Brigotti et al. found that a quasi-non-toxic concentration of the bacterial toxin Stx1 potentiates the cytotoxic action of mafosfamide on a Burkitt lymphoma cell line, namely Raji (Brigotti et al., 2013).

Various bacterial toxins have been genetically fused or chemically conjugated to ligands that bind to cancer cells. Immunotoxins are engineered chimeric proteins that consist of an antibody or carrier ligand coupled to a modified plant or bacterial toxins. These fusion proteins can bind specifically to target cells. A wide variety of immunotoxins have been tested against a wide variety of malignancies in cell culture, in animal models, and in patients. The most useful of these agents appear to be the relatively small recombinant fusion toxins that contain either growth factor or Fv fragments as ligands (Kreitman, 2006). At present, immunotoxins, which contain human interleukin-2 and truncated diphtheria toxin, are approved for use in cutaneous T-cell lymphoma (Wood, 2014). Another, containing an anti-CD22 Fv and truncated Pseudomonas exotoxin, has induced complete remissions in a high proportion of cases of hairy-cell leukemia (Bachran et al., 2013).

Clinical application of staphylococcal enterotoxin C2 (SEC2) was restricted during the cure of malignant tumor due to its side-effects. Through truncation of SEC2, it would efficiently solve the question of SEC2 side-effects. Novel truncated staphylococcal enterotoxin C2 mutant, which could efficiently inhibit the growth of tumor cells, can become novel anti-tumor agents with the lowest side-effects and best treatment effects in clinic (Hui et al., 2011).

Bacillus Calmette-Guerin and staphylococcal enterotoxin B showed similar anti-angiogenic effects. Bacillus Calmette-Guerin plus enterotoxin treatment had additional activity compared to that of monotherapy. It was more effective in restoring apoptosis and balancing cellular proliferation, and it correlated with increased endostatin, and decreased vascular endothelial growth factor, matrix metalloproteinase-9, Ki-67 and insulin-like growth factor receptor-1 reactivity (Reis et al., 2012). According Bandala et al., botulinum toxin A, which is widely known as its relaxing effect on skeletal muscles, exerted great cytotoxic activity in the T47D breast cancer cell line via apoptotic processes caspase-3 and -7. It can be suggested that BtxA treatment may be used as an alternative treatment against breast cancer (Bandala et al., 2013).

Conclusion and Future Prospects

Previous description has shown that different components of biotoxins have antitumor activity in various in vitro or animal models, as well as in clinical studies and they can be used as a natural therapeutic agent against cancer. Some of the included molecules are under clinical trial and may find application for anticancer drug development in the near future. Since there is controversy about the cytotoxic effect of the venom, many new technologies have been applied to reduce toxicity. Tagging of the venom with polymeric materials, such as liposomes, microspheres, hydrogels and nanoparticles for targeting the cancer cells can be one of the best therapeutic approaches for the treatment of cancer.

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