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Venom as therapeutic weapon to combat dreadful diseases of 21st century: A systematic review on cancer, TB, and HIV/AIDS

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ABSTRACT

Cancer and infectious diseases are the preeminent causes of human morbidities and mortalities worldwide. At present, chemotherapy, radiotherapy, immunotherapy, and gene therapy are considered as predominant options in order to treat cancer. But these therapies provide inadequate consequences by affecting both the normal and tumor cells. On the other hand, tuberculosis (TB), and HIV (human immunodeficiency virus) infections are significant threats, causing over a million mortalities each year. The extensive applications of antibiotics have caused the microbes to acquire resistance to the existing antibiotics. With the emerging dilemma of drug resistant microbes, it has become imperative to identify novel therapeutic agents from natural sources as emphatic alternative approach. Over the past few decades, venoms derived from several reptiles, amphibians, and arthropods including snakes, scorpions, frogs, spiders, honey bees, wasps, beetles, caterpillars, ants, centipedes, and sponges have been identified as efficient therapeutics. Venoms constitute plethora of bioactive components, particularly peptides, enzymes, and other chemical entities, which exhibit a large array of anticancer and antipathogenic activities. This review highlights the panorama of bioactive components of animal venoms divulging the anticancer, anti-tubercular, and anti-HIV activities. In a nutshell, this context discloses the decisive role of animal venoms as alternative natural resources to combat these deadly diseases of 21st century, and propounding the plausible development of new therapeutic drugs in the present era.

1. Introduction

Considering the devastating threats of dreadful diseases, mankind has been exploiting natural resources as potential therapeutic agents since ancient periods. A variety of deadly infections had been treated and humans were able to get rid of those dreadful diseases permanently. However, from past few decades, we are desperately looking for the plausible treatment for few life-threatening diseases that are affecting the society rapidly. At present, cancer, tuberculosis (TB), and HIV (human immunodeficiency virus)/AIDS (acquired immunodeficiency syndrome) are one of the deadliest diseases and are undoubtedly the foremost causes of mortalities in 21st century.

Cancer is a multi-cellular and multi-genic disease that is in fact the colossal public burden globally. In cancer, the alteration in the activation, expression, and localization of gene-regulatory proteins inside cells cause genetic manipulation, thereby influencing the signalling pathways and allowing the uncontrolled cell growth. According to the recent Global Cancer Statistics, there are approximately 32.6 million cancer patients globally, representing it as one of the primary causes of mortality in the world [1]. Diversified therapies such as chemotherapy, radiotherapy, and immunotherapy have been used in order to treat cancer. In spite of the limited success of chemotherapy, this method of treatment is being avoided due to resistivity after some time [2]. On the other hand, radiotherapy/radiation therapy shows approximately 40% of cancer cure by declining the multiplication property of tumor cells [3]. Unfortunately, the radiotherapy for cancer treatment is affecting normal cells too and causing either acute or late radiation toxicity [4]. Over the past few years, the treatment of cancer by immunotherapy is considered as efficacious approach which is used in the early stage of the tumor growth. Immune targets do not play a paramount role in the life or death of the cancer cells since they serve only to direct immune effectors to the tumor cells [5]. It primarily empowers the immunity for

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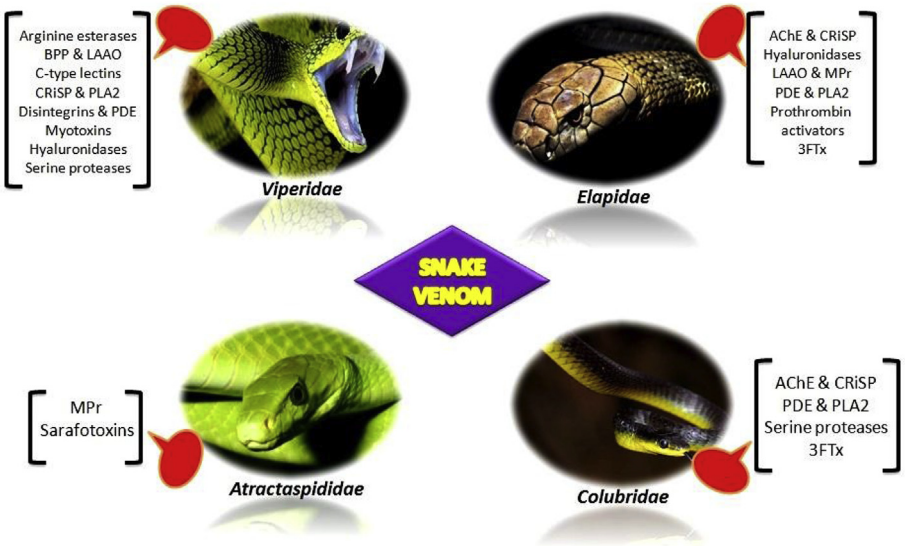


Fig. 1. Composition of venoms extracted from snakes of families Viperidae, Elapidae, Atractaspididae, and Colubridae. (BPP - Bradykinin-potentiating peptides; LAAO - L-amino acid oxidases; CRiSP - Cysteine-rich secretory proteins; PLA2 - Phospholipase A2; PDE - Phosphodiesterases; AChE - Acetylcholinesterases; MPr - Metalloproteinases; and 3FTx - Three-finger toxins).

overcoming the cancer cells rather than killing tumor cells. In view of the inadequate impact of above mentioned therapies, it led to investigate new strategies for cancer treatment.

Tuberculosis is one of the deadliest bacterial infections which cause millions of deaths annually. This tropical disease is mainly caused by *Mycobacterium tuberculosis* (Mtb), which particularly infects human macrophages. About 10.4 million new TB cases were reported globally based on the latest statistical data of World Health Organization (WHO), 10% of which were co-infected with HIV [6]. In spite of significant decrease in the TB cases since 2000, the sheer counts of deaths and the emergence of multi-drug resistant TB (MDR-TB), extensively-drug resistant TB (XDR-TB), totally drug resistant TB (TDR-TB), and co-infection with HIV are the huge despondency towards the End-TB strategy.

Since the onset of the epidemic, more than 70 million people have been infected with HIV and about 35 million people have died of AIDS. Surprisingly, at the end of 2016, about 36.7 million people were reported to be infected with HIV worldwide. The statistical analyses show that the epidemics of HIV fluctuate considerably between countries and regions. Sub-Saharan Africa represents most severely affected, with nearly 1 in every 25 adults infected with HIV, thereby accounting for about two-thirds of the patients living with HIV globally [7]. Unfortunately, there is lack of efficacious vaccine for eliminating the transmission of HIV. However, vaccines such as the Merck STEP [8] and the Thai RV144 [9] confirmed that development of a prophylactic HIV vaccine still requires extensive research. The current scenario undeniably manifests the inevitability of identifying new anti-HIV agents which can be employed for preventing HIV/AIDS dissemination.

In order to combat the epidemics of deadly diseases, there is an essentiality to identify efficacious agents with novel mode of actions from un/less exploited natural sources [10,11]. In view of this, at present, animal's derived venoms are receiving enormous attention among scientific communities. Interestingly, venoms from snakes, toads, spiders, and scorpions have been exploited for millennia in several conventional therapies in order to treat a variety of ailments. However, the traditional therapy represented the utilization of lower doses of whole venoms for attaining their medicinal roles. In contrary to this, the modern therapy adopts comparatively more rigorous approach to exploit venoms as therapeutics [12].

Venoms are the poisonous secretions which are produced by specialized glands associated with teeth, stings, and spines of respective animal. Animal venoms are mixture of bioactive molecules that can undeniably be potential agents for the development of auspicious therapeutic drug. The composition of venom differs from animal to animal, but most of the venoms are a heterogeneous mixture of inorganic salts, low molecular weight organic molecules, peptides, and enzymes [13]. Despite the toxicity of venoms, they can be exploited to study the physiological and pathological mechanisms and represent promising bioactive components. Hence, it is not surprising at all that recent researches are focussed on the identification of leading constituents from venoms for developing new therapeutic drugs with novel mechanism of actions.

2. Venoms as therapeutic agent against cancer

The isolation of propitious cancer specific components from animal associated venoms was one of the appealing developments in oncology. Surprisingly, tremendous variation and molecular diversity of venoms have created new avenues for future oncology researchers. Among discrete anticancer agents in targeted therapies, cancer-specific peptides from animal venoms have created tremendous interest to use as templates for designing new efficacious anticancer drugs.

2.1. Snake venom

Snake venoms are variegated mixture of enzyme, toxins, nucleotides, inorganic cations, proteinaceous, and peptidyl toxins. However, about 90% of venom's dry weight is proteinaceous in nature which has medicinal importance. Additionally, it is a vast sources of neurotoxic, cardiotoxic, cytotoxic, and diverse other active components. Different species of snakes have distinct varieties of venom depending upon its location, habitat, age etc. Most interestingly, the concentration of secreted venom from glands depends upon the climate and season. Fig. 1 shows the disparate active components present in important snake families.

Hyaluronidase is one of the proteinaceous constituents that catalyzes beta- N- acetyl- glucosaminidic linkages in HA polymer. It is an endoglycosidase and exhibit promising activity at around pH 8. This enzyme is mainly known for damaging the extracellular matrix at the site of bite. L-amino acid oxidase (LAAO) is also called as ophio- amino-acid oxidase and catalyzes the steriospecific oxidative deamination of an L-amino acid substrate, corresponding to a ketoacid with hydrogen peroxide and ammonia production. It belongs to oxidoreductase family and represents 1–9% of total venom proteins. Phospholipase A2 (PA2) is the leading constituents of snake venoms which display assorted toxicity such as neurotoxicity, cytotoxicity, cardiotoxicity, hypotensive, and pro-inflammatory effects. Cholinesterase is known to target the nervous system. The exogeneous cholinesterase can be used as an

Table 1
Various snakes associated anticancer proteins and their mechanisms of action.

Snake	Family	Proteins	Anticancer mechanism	References
Crotalus atrox	Viperidae	VAP1, VAP2	Induces apoptosis of HUVEC	[31,32]
Vipera lebetina	Viperidae	VLAIPs	Inhibits proliferation and induces apoptosis of HUVEC	[33]
Trimeruserus flavoviridis	Viperidae	HV1	Inhibits adhesion of HUVEC and induces apoptosis	[34]
Trimeresurus gramineus	Viperidae	Graminelysin	Inhibits proliferation and induces apoptosis of HUVEC	[35]
Bothrops alternatus	Viperidae	BaG	Inhibits adhesion of K562 cells	[36]
Trimeresurus stejnegeri	Viperidae	TSV-DM	Inhibits cell proliferation and induces transient cell morphologic changes of endothelial cells	[37]
Gloydius halys	Viperidae	Halysase	Inhibits proliferation and induces apoptosis of HUVEC	[38]
Agkistrodon acutus	Viperidae	Accurhagin-C	Prevents migration and invasion of endothelial cells	[39]
Agikistrodon rhodostoma	Viperidae	Rhodostomin	Inhibits cell migration and angiogenesis	[40]
Trimeresurus flavoviridis	Viperidae	Triflavin	Inhibits adhesion of tumor cells to matrix proteins, cell migration, and angiogenesis	[41]
Macrovipera lebetina	Viperidae	Lebestatin	Inhibits migration and angiogenesis	[42]
Eritocophis macmahoni	Viperidae	Eristostatin	Inhibits cell motility	[43]
Bothrops alternatus	Viperidae	DisBa-01	Anti-angiogenic and antimetastatic effect	[44]
Macrovipera lebetina	Viperidae	Leberagin-C	Inhibits cell adhesion of melanoma tumor cells	[45]
Agkistrodon acutus	Viperidae	Accutin	Inhibits angiogenesis *in vitro* and *in vivo*	[46]
Macrovipera lebetina	Viperidae	MVLPLA2	Inhibits adhesion and migration of human microvascular cells and inhibits angiogenesis	[47]
Bothrops jararacussu	Viperidae	Bth-A-IPLA2	Anti-tumor activity on adenocarcinoma and leukaemia cells	[48]
Cerastes cerastes	Viperidae	CCPLA2-1	Inhibits migration and adhesion of fibrosarcoma and melanoma cells	[49]
Echis multisquamatus	Viperidae	EM16	Inhibits adhesion and migration of HUVEC cells	[50]
Bothrops jararacussu	Viperidae	BJcuL	Inhibits tumor cell and endothelial cell growth	[51]
Macrovipera lebetina	Viperidae	Lebecetin, lebectin	Inhibits adhesion, migration, and invasion of human tumor cells. Inhibits angiogenesis	[52]

efficient therapeutics for treating several diseases due to its great reactivity towards organophosphorus components. On the other hand, thrombin-like enzymes act as anticoagulants *in vivo* and *in vitro*. These enzymes have got more attention due to their action as defibrinating agent. Some examples of thrombin-like enzymes are carotalase, ancrod, and batroxobin which can be purified from snake venoms. Carotalase plays a pivotal role in the fibrin formation in burns in the animals. Ancrod and batroxobin have been employed to remove the fibrinogen [14].

Vipera lebentina turnica toxin is known to induce apoptotic cell death of ovarian tumor cells by inhibiting NF-kB and STAT3 signal, followed by p50 and p65 translocation inhibition into the nucleus. It not only up-regulates the expression of pro-apoptotic protein Bax and Caspase-3 but also down-regulates the anti-apoptotic protein Bcl-2 [15]. The crude venoms of Indian monocellate Cobra (*Naja kaouthia*) and Russell's viper (*Vipera russelli*) were investigated to determine the anticancer properties against sarcoma, carcinoma, and leukemia models. The *in vivo* results showed increased life span of EAC (Ehrlich ascites carcinoma) mice. On the other hand, venom exhibited promising *in vitro* cytotoxic and apoptogenic properties on human leukemic cells (U937/K562). It showed significant reduction in the rate of cell proliferation, and also caused cellular morphological changes [16]. In another investigation, da Silva et al. [17] reported that the anticancer activities of *Bothrops jararaca* and *Crotalus durissus terificus* associated venoms might be probably because of indirect aspect of inflammatory responses induced by IL-2, IL-8, and TNF-α. According to Yang et al. [18], the anticancer trait of *Naja atra* derived Cardiotoxin-3 (CTX-3) induced apoptotic cell death accompanied by up-regulation of Bax and endonuclease G, and down-regulation of Bcl-x in K562 cells which was further confirmed by DNA fragmentation. Protein toxins (drCT-1) isolated from Indian Russells viper (*Daboia russelli russelli*) venom exhibited anticancer properties. In the very study, drCT-2 protein toxin showed antineoplastic activity [19]. Disintegrins are non-enzymatic proteinaceous components that are known to possess anticancer activity by inhibiting cell-cell interactions, cell-matrix interactions, and signal transduction. Kang et al. [20], reported the growth inhibition of metastatic tumor and solid tumor in mice by salmosin (Korean snake venom associated disintegrin). Cobra venom associated phospholipase (a lipolytic enzyme) has anticancer property and it hydrolyses the fatty acyl ester at the sn-2 position of membrane phospholipids [21]. Phospholipase A2 as well as Phospholipase B from *Bothrops newweidii* and Australian elapid snake venom was toxic to rhabdomyosarcoma cells [22] and B16 F10 melanoma cells, respectively [23]. The anticancer activity of Contortrostatin (present in southern copperhead snake venom) was reported on OVCAR-5 (human epithelial carcinoma cell line of ovary) cells. It inhibits cancer cells invasion by blocking the OVCAR-5 cells adhesion to varied extracellular matrix proteins [24]. *Ophiophagus hannah* venom derived LAAOs reduced the uptake of thymidine in murine melanoma, fibrosarcoma, colorectal cancer, and Chinese hamster ovary cell line [25]. Crotoxin, isolated from a South American snake (*Crotalus durissus terrificus*) venom, is a cytotoxic PLA2 component [26]. Crotoxin (a cytotoxic PLA2 component) showed *in vitro* anticancer trait against several murine and human tumor cell line [27]. According to the reports of Al-Sadoon et al. [28], human breast cancer cell line proliferation can be reduced by *Walterinessia aegyptia* venom, individually or mixed with silica nanoparticles. The treatment showed reduction in the Bcl-2 expression and increased caspase-3 activation. Most importantly, actin polymerization and cytoskeletal rearrangement were significantly reduced due to the treatment, without affecting the normal cells. BJcuL from *Bothrops jararacussu* venom exhibited anticancer effect on gastric carcinoma cells MKN45 and AGS [29]. Naumann et al. [30] reported the anticancer property of *Bothrops leucurus* venom associated LAAOs on stomach cancer MKN-45, adenocarcinoma HUTU, colorectal RKO, and human fibroblast LL-24 cell lines. Besides above mentioned reports, Table 1 shows the promising anti-tumor role of varied proteins isolated from diverse snake venoms.

2.2. Scorpion venom

Scorpion venoms have been extensively used since ancient period in the traditional therapies of various countries, particularly India, China, and Africa in spite of the adverse influence of venoms on the human populace. Scorpion venom is a complex mixture of diversified biological constituents viz. proteinaceous components, mucopolysaccharides, phospholipases, hyaluronidases, protease inhibitors, serotonin, histamine, histamine-releasing peptides, nucleotides, inorganic salts, mucus, free amino acids, lipids, heterocyclic components, neurotoxic peptides, and several other unknown constituents. *In vitro* and *in vivo* investigations have revealed the promising anticancer trait of scorpion venom against varied tumors such as glioma, neuroblastoma, leukemia, lymphoma, breast, lung, and prostate because of apoptotic, antiproliferative action coupled with the induction of cell cycle arrest, and inhibition of cancer progression [53].

Chlorotoxin (Cltx) is one of the most active peptides isolated from

Leiurus quinquestriatus. It is known to inhibit chloride influx process in glioma cells membrane, without affecting the normal cells [54]. It binds with MMP-2 endogenously expressed by glioma cells [55]. Loss of gelatinase activity, disruption in chloride channels currents, reduced MMP-2 and chloride channel expression, and chloride channels internalization are caused due to its exposure [55]. Chlorotoxin may act as brain tumor-specific marker in cancer therapy. BMK-CBP is a serine proteinase-like protein which is extracted from Chinese red scorpion venom (*Buthus martensii* Karsch). It binds with MCF-7 cell line, and revealed the cell binding characteristic at varied concentrations [56]. BmHYA1, a hyaluronidase isolated from *B. martensi* converted hyaluronic acid into smaller oligosaccharides, and caused the modulation of CD44 expression and cell surface markers in breast cancer cell line [57]. Charybdotoxin (CTX) was isolated from *Leiurus quinquestriatus* venom and it showed depolarization in human breast cancer cells, thereby arrested the cells in the early G1, late G1, and S phases [58]. Bengalin was isolated from Indian Black scorpion (*Heterometrus bengalensis*) venom and it revealed antitumor property against U937 and K562 cells, thereby indicating that this protein might provide putative molecular process for their tumoricidal impact on leukemic cells, might be mediated by mitochondrial death cascade [59].

In another report, BmKn-2 scorpion venom peptide and its derivatives were used for determining antitumor properties against human oral squamous cells carcinoma cell line (HSC-4). Findings revealed that the anticancer activity was due to the apoptosis induction, as further observed using phase contrast microscopy and RT-PCR tools. The microscopy studies showed shrinkage as well as rounding traits in treated HSC-4 cells. On the other hand, RT-PCR assay exhibited improved pro-apoptotic genes (caspase-3, -7, and -9) expression and decreased mRNA range of anti-apoptotic BCL-2 [60].

A remarkable reduction in tumor cells was observed when *Mesobuthus gibbosus* associated proteases were tested against human lung adenocarcinoma (A549) cell lines, thereby revealing considerable cytotoxic and gelatinolytic properties [61]. Likewise, peptide TRAIL (TNF-related apoptosis-inducing ligand) isolated from scorpion venom induced apoptosis in melanoma cells, and causes the permeabilization and depolarization of mitochondrial outer membrane and membrane potential, respectively, thereby releasing the varied mitochondrial constituents which cause inhibition of melanoma cells proliferation and induces apoptosis [62].

In general, scorpion venoms exhibit anti-tumor potential mainly by inducing cell cycle arrest, growth inhibition, apoptosis, angiogenesis inhibition, invasion as well as metastasis inhibition, and blocking specific transmembrane channels. Table 2 shows the anticancer potency of diverse scorpion venoms against various cancer cell lines, thereby representing their ample role in cancer therapy (adapted from Raposo [63]).

2.3. Beetle and honey bee venom

Canthardin, a monoterpene derived from *Mylabris phalerata* and *M. cichorii* (Chinese blister beetles) had been reported to exhibit *in vitro* anticancer activity against human leukemic cells [64]. Canthardin derivatives have also been known to inhibit the growth of varied cancer cell lines such as prostate, oral, colon, cervical, and gall bladder [65–70]. Phosphoprotein phosphatase 1 and 2A are mainly inhibited by canthardin, thereby causing DNA damage and apoptosis. The blocking of oxidative stress-independent growth in pancreatic cancer cells is induced by canthardin by arresting G2/M cell cycle and apoptosis [71].

According to the report of Huang et al. [72], canthardin affects human colorectal tumor growth in time- and concentration-dependent manner. The CDK1 kinase activity was reduced mainly because of the exposure of cantharidin which led blocking the progress of cells from G2 to M phases. Additionally, apoptosis was observed to be a key factor for inhibiting the growth of colorectal tumor cells. In another investigation of Huang et al. [73], the anticancer activity of cantharidin against human bladder carcinoma cells was reported due to the blockage of the gene expression, protein concentrations, and matrix metalloproteinase −2 (MMP-2) or MMP-9 activities. Shou et al. [74] reported the anticancer trait of cantharidin against breast cancer cell lines. The exposure of cantharidin caused apoptosis as well as growth reduction, adhesion, and migration of the tumor cells. Dang and Zhu [75] had synthesized cantharidin solid lipid nanoparticles as drug carriers in order to get rid of its toxicity, low solubility, and short half-life in cancer therapy.

Bee venom constitutes several bioactive components viz. melittin, apamin, adolapin, mast-cell-degranulating peptide, PA2, histamine, and epinephrine. Melittin and PA2 have been widely exploited for targeting a number of tumor cells. According to Moon et al. [76], bee venom induced apoptosis in human leukemic U937 cells. Melittin (*Apis mellifera* derived peptide) was observed to exhibit growth inhibitory effect on hepatocellular carcinoma by affecting the motility and migration via suppressing Rac-1 dependent pathway [77]. Bee venom may inhibit growth of breast cancer cells by blocking Cyclooxygenase-2 (COX-2) expression and pro-inflammatory cytokines production [78].

2.4. Spider venoms

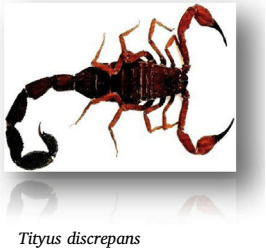
Anticancer property of Latarcins (a linear cytolytic peptide venom from *Lachesana tarabaevi*) had been reported [79]. In another report, Latarcin 2a (Ltc2a) exhibited *in vitro* cytotoxicity against human erythroleukemia (K562) cells by penetrating, forming pores in the membrane, and inducing membrane blebbing, thereby causing swelling, followed by death of K562 cells [80]. Surprisingly, the peptide was unable to induce apoptosis.

Lycosin-1 (a peptide isolated from *Lycosa singoriensis* venom) exhibited *in vitro* inhibition of various human cancer cells growth such as fibrosarcoma (H1080), lung adeno-carcinoma (H1299 and A549), prostate carcinoma (DU145), colon adenocarcinoma (HCT-116), cervix carcinoma (HeLa), and hepatocellular carcinoma (HepG2) [81]. In contrast, Lycosin-1 showed lower *in vitro* growth inhibition of non-cancerous human liver (L02) cells, non-transformed mouse skin epidermal (JB6) cells, and erythrocytes. Activation of intrinsic apoptosis, up-regulation of P27, and inhibition of cell proliferation were reported as common mode of action of Lycosin-1 against tumor cells. Further, dose dependent *in vivo* anticancer studies of Lycosin-1 was carried out in human A549, H1299, and HeLa xenograft-bearing nude mice, which revealed chromosomal condensation and nuclear shrinkage in treated cancer cells. In addition to this, the peptide induced apoptosis and it was confirmed by TUNEL staining.

Venom extracted from *Macrothele raveni* spider effectively suppressed the growth of human myelogenous leukemia (K562) cells at varied concentrations and showed reduced toxicity on human lymphocytes, thereby suggesting the selective inhibitory property of particular venom against leukemia cells only. The nuclei condensation, DNA fragmentation, and caspase-3 as well as caspase-8 activation were observed as common growth inhibitory mechanism of venom against K562 cells [82]. Antitumor studies of *M. raveni* venom were conducted against human breast carcinoma (MCF-7) [83]. In another study, *in vivo* anticancer activity of *M. raveni* venom was observed against human cervix carcinoma (HeLa)-bearing nude mice. The treatment caused marked reduction in tumor cells size and depicted morphological alteration, inhibition of proliferation, and up-regulation of caspase-3 [84].

Venom extracted from *Phoneutria nigriventer* spider (PNV) constitutes peptides that influence calcium, potassium, and sodium ion channels [85]. Furthermore, these peptides had an analgesic impact in a cancer pain model [86]. Blood-brain barrier (BBB) permeabilization is changed by PNV [87] and selectively affects astrocytes. It had been reported that PNV induced edema in astrocyte end-feet [87] and increased glial fibrillary acidic protein (Gfap), S100 [88], aquaporin-4 [89], and connexin 43 (Cx43) [90] in rat astrocytes *in vivo* and/or *in*

Table 2
Anticancer properties of active components extracted from diverse scorpion species venoms.

Scorpion species	Active component	Cell lines	Mode of action
 *Buthus martensii* Karsch (BmK)	Whole venom	Human glioma (U251-MG), Human lymphoma (Raji and Jurkat), Human breast cancer (MCF-7), and Human hepatoma (SMMC7721)	Up-regulation of caspase 3, arresting cell cycle on G0/G1; decreasing Cyclin D1; and increasing PTEN, p27
	PESV	Human leukemia (K562), Murine hepatoma (H2-2), and Human lung (A549)	Decreasing PI3K, Akt, increasing PTEN, arresting cell cycle on G0/G1 phase, decreasing mTOR, reducing VEGF, and decreasing microvessel density
	BmKKx2	Human myelogenous leukemic (K562)	Blocking K^{2+} channels, suppressing proliferation, inhibiting differentiation, promoting differentiation dependent apoptosis
	BmKn-2	Human oral squamous carcinoma (HSC-4) and Human mouth epidermoid carcinoma (KB)	Increasing caspase-3, -7, -9, decreasing Bcl-2, and increasing p53 and BAX
	LMWSVP	Human hepatoma (SMMC7721)	Increasing caspase-3, and decreasing Bcl-2
	TM-601	Rat glioma (F98) and Human glioblastoma (U87)	Blocking Cl^{-}channel
 *Heterometrus bengalensis* Koch	Whole venom	Human leukemic (U937 and K562)	Arresting cell cycle, inducing membrane blabbing, condensation of chromatin, and degradation of DNA
	Bengalin	Human leukemic (U937 and K562)	Inducing DNA fragmentation, decreasing telomerase activity, loss of mitochondrial membrane potential, and activating caspase-3, 9
 *Androctonus amoreuxi*	Whole venom	Ehrlich ascites and solid tumors, and Human breast cancer (MCF-7)	Increasing caspase-3, inducing DNA fragmentation, reducing VEGF, decreasing cell motility, and colony formation
 *Odontobuthus doriae*	Whole venom	Human neuroblastoma (SH-SYSY) and Human breast (MCF-7)	Inducing mitochondria depolarization and increasing caspase-3
 *Tityus discrepans*	Whole venom	Human breast (SKBR3)	Inducing FasL expression and DNA fragmentation

(*continued on next page*)

Table 2 (*continued*)

Scorpion species	Active component	Cell lines	Mode of action
 *Androctonus crassicauda*	Whole venom	Human neuroblastoma (SH-SYSY), Human breast cancer (MCF-7), Human ileocecal adenocarcinoma (HCT-8), Human colorectal carcinoma (HCT-116), and Human breast carcinoma (MDA-MB-231)	Increasing caspase-3, arresting cell cycle on S-phase, depolarizing mitochondrial membrane, and decreases cell motility and colony formation
 *Androctonus bicolour*	Whole venom	Human breast carcinoma (MDA-MB-231)	Decreasing cell motility and colony formation
 *Leiurus quinquestriatus*	Whole venom Chlorotoxin (CTX) GST-CTX CTX-modified liposomes	Human breast carcinoma (MDA-MB-231) Human glioma (D54-MG, CCF-STTG-1) and Human pancreatic carcinoma (PANC-1) Rat glioma (C6) Human glioblastoma (U87), Human lung carcinoma (A549), and Murine breast (4T1)	Decreasing cell motility and colony formation Inhibiting/reducing MMP-2, and inhibiting Cl^-currents Inhibiting/reducing MMP-2, inhibiting Cl^- currents Inhibiting/reducing MMP-2, inhibiting cell migration, and inhibiting Cl^-currents
 *Buthus tamulus*	Iberiotoxin (IbTX)	Human glioma (U87-MG)	Blocking K^+ channels
 *Tityus serrulatus*	TiTx gamma TsIV-5	Mouse neuroblastoma (NIE115) Mouse neuroblastoma (N18)	Affecting Na^+ channels Blocking Na^+ current

vitro. In general, these peptides can target glioma cells, which are developed from glia cells, and especially transformed astrocytes [91].

2.5. Venoms from other arthropods

Besides the anticancer potentialities of venoms from snakes, scorpions, beetles, honey bees, and spiders, few arthropods and amphibians have also been known to produce venoms comprising antitumor characteristics. Fig. 2 depicts the anticancer role of venoms extracted from potent wasp species against various cancer cell lines. The wasp venoms showed antitumor activity through varied mode of actions viz. depolarization, irreversible cytolysis, tumor cell proliferation inhibition, membrane disruption, morphological alteration, apoptosis, nuclear chromatin condensation, cell cycle arrest, and mRNA expression inhibition.

Fig. 3 shows the anticancer properties of venoms extracted from specific species of toads, centipedes, caterpillars, and ants against various cell lines. The dried white secretion from skin glands of *Bufo gargarizans* showed anticancer property against human bladder carcinoma cell line by exhibiting caspase 3 and caspase 9 proteolytic activations [92]. In another study, Qiao et al. [93] revealed *in vitro* cytotoxicity of active component of *B. gargarizans* secretion. Das et al. [94] and Giri and Gomes [95] demonstrated antineoplastic activity of the skin extract from *Bufo melanostictus* on EAC cells and human leukemic cell lines through cell cycle arrest mechanism. Brevinin 2R, extracted from *Rana ridibunda*'s skin showed promising toxicity towards diversified cancer cell lines. The anticancer property was mainly due to the pro-apoptotic molecules over-expression, mitochondrial membrane potential

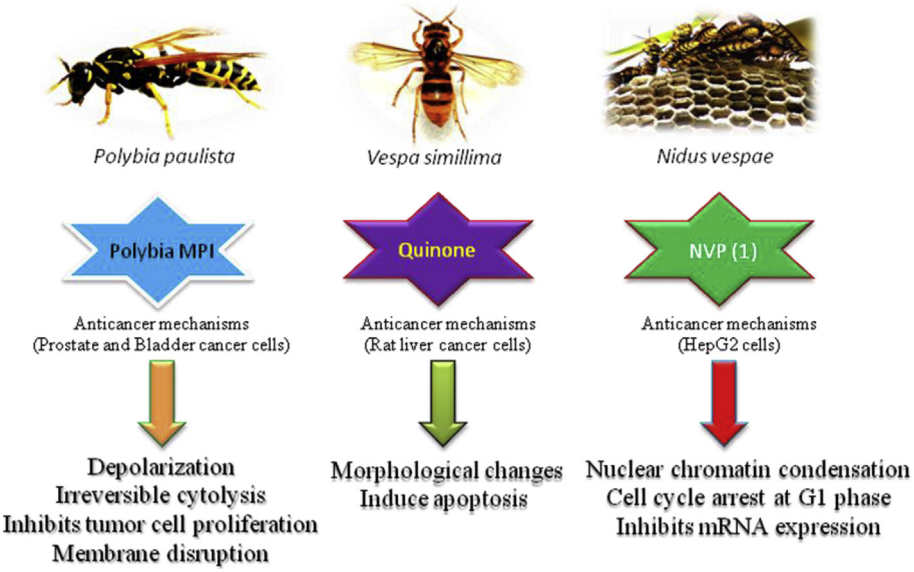


Fig. 2. Anticancer characteristics of potent wasp venoms against various cell lines and their mechanisms of action.

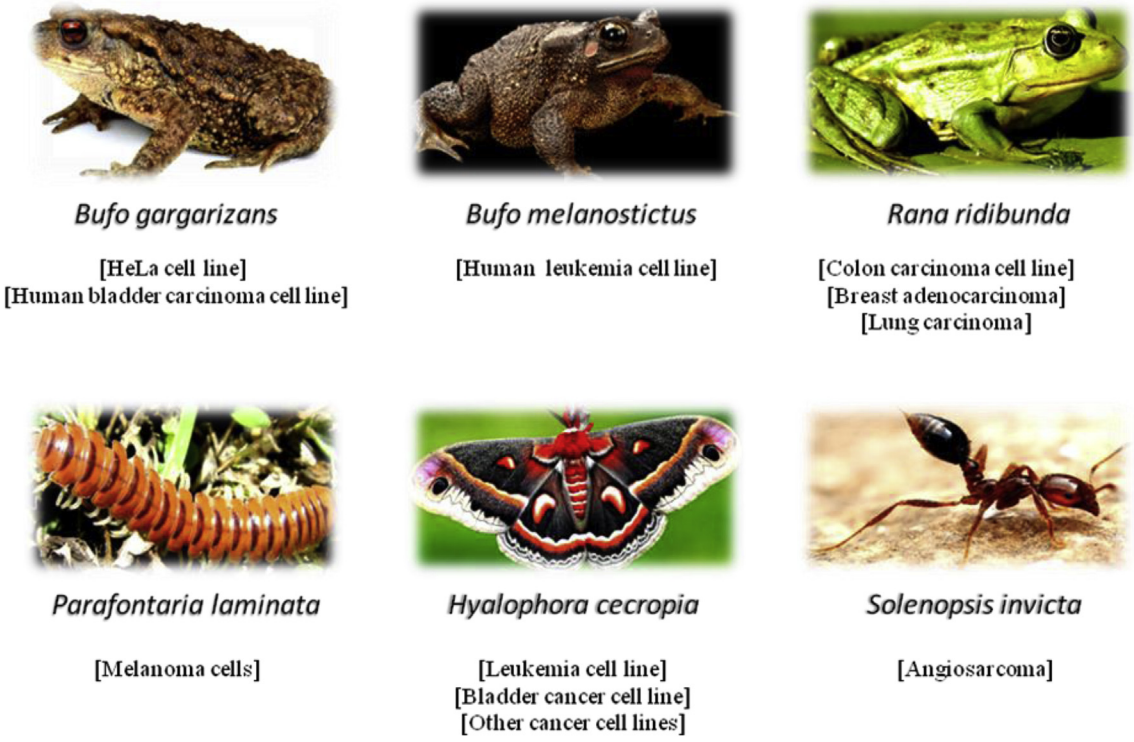


Fig. 3. Anticancer properties of venoms extracted from specific species of toads, centipedes, caterpillars, and ants against various cell lines.

reduction, and reactive oxygen species increment. Additionally, Brevinin 2R treatment caused autophagosome, thereby suggesting the involvement of lysosomal-mitochondrial death pathway [96].

Sonoda et al. [97] reported the anticancer activity of *Parafontaria laminata* associated Manb (1–4) [Fuca (1–3)] Glcb 1-Cer, (glycosphingolipid-7) against melanoma cells. This synthetic compound showed tumoricidal impact on melanoma cells by suppressing focal adhesion kinase (FAK)-Akt pathway as well as extracellular signal regulated kinase (Erk) 1/2 pathways.

Cecropins (group of peptides isolated from *Hyalophora cecropia* hemolymph) showed *in vitro* tumoricidal effect towards varied mammalian tumors. Further *in vivo* reports showed that cecropin has the ability to increase the survival period of mice bearing murine ascitic colon adenocarcinoma cells [98]. Likewise, Suttmann et al. [99] reported that cecropin A and B had the potency for inhibiting the bladder cancer cells proliferation by disrupting cell membrane, thereby causing irreversible cytolysis. According to the reports of Bai et al. [100], solenopsin A, an alkaloid isolated from *Solenopsis invicta,* exhibited antiangiogenic property by inhibiting a series of kinases.

3. Venoms as therapeutic agent against TB

Currently, there is an uncontrollable emergence of drug resistant Mtb due to over exploitation of commercially available antibiotics. In general, Mtb has unique characteristics to develop several adaptive strategies for destructing the phagosomal pathways, thereby surviving

inside the macrophage. Over the last few decades, a number of mycobactericidal agents are under varied phases of pre-clinical and clinical trial tests in order to get rid of this devastating disease. According to the recent studies, animal toxins have been proved as promising anti-tubercular agents and offered a great hope for mankind. Despite the toxicity of venoms, they have been reported as pronounced therapeutic agents.

According to the reports of Bhunia et al. [101], venoms extracted from *Naja naja*, *Bungarus fasciatus*, *Daboia russelli russelli*, and *Naja kaouthia* exhibited potential anti-tubercular activity against MDR-TB. Among all the tested venoms, *N. naja* and *N. kaouthia* associated venoms showed significant inhibition of MDR-TB growth for a longer period. In another *in vitro* study, vgf-1 (a small peptide isolated from *Naja atra* venom) revealed anti-tubercular activity against MDR-TB [102]. Pandinin 2 (Pin2), an antimicrobial peptide isolated from *Pandinus imperator*'s (a scorpion) venom showed better growth inhibitory activity at molar concentrations against Mtb than that of the conventional antibiotics such as ethambutol, isoniazid, and rifampicin [103]. Figueroa-Montiel et al. [104] demonstrated the anti-tubercular activity of a new molecular entity, isolated from *Conasprella ximenes*'s venom gland. The minimum inhibitory concentration of conotoxin was observed more or less similar to the conventional antibiotics used, thereby revealing the potency of Conidea venom as a therapeutics against TB.

In spite of limited investigations on mycobactericidal activity of animal's venom, these bioactive components of venoms have enlightened a new hope for the plausible development of future anti-tubercular drugs with novel mode of actions (Fig. 4). Extensive studies on anti-tubercular role of venoms require further attention in order to combat deadly emergence of drug resistant Mtb in future.

4. Venoms as therapeutic agent against HIV

Few commercially available antiviral drugs induce drastic effects, particularly to those patients undergoing HIV treatment. The development of novel antiviral agents from natural resources is the urgent call for this hour. Among diversified natural resources, animal's venom has been reported to reveal enormous characteristics as anti-HIV agents.

4.1. Snake venoms

Alrajhi and Almohaizeie [105] demonstrated the virucidal property of snake venoms against multidrug-resistant HIV as antiretroviral therapy in clinical practice. This antiretroviral process caused reduction in virus count and elevation in T CD^{4+}. Further, the study reported the activity because of the active venom components that are homologous to HIV-1 glycoprotein (gp) or proteases [105]. Zhang et al. [106] showed improvement in anti-HIV property by linking the gp120 fragment to the HIV peptide fusion inhibitors. The LAAOs are well known for exhibiting anti-HIV traits [107]. TSV-LAO, characterized from *Trimeresurus stejnegeri* venom associated TSV-LAO was the first snake venom LAO to reveal antiviral property at varied doses, and showed activity at lower concentrations by inhibiting the formation of syncytium and HIV-1 p24 antigen expression [108]. Phospholipases A2 shows anti-HIV property by interacting host cells and preventing the release of capsid protein, thereby blocking viral entry into the host cells [109,110]. Phospholipases A2 NmmCMIII from *Naja mossambica*, taipoxin from *Oxyuranus scutellatus*, and nigexine from *Naja nigricollis* also showed antiviral activity against HIV [111]. Metalloprotease inhibitors extracted from snake venoms showed anti-HIV activity by preventing the new HIV particles production and by inhibiting the viral proteases

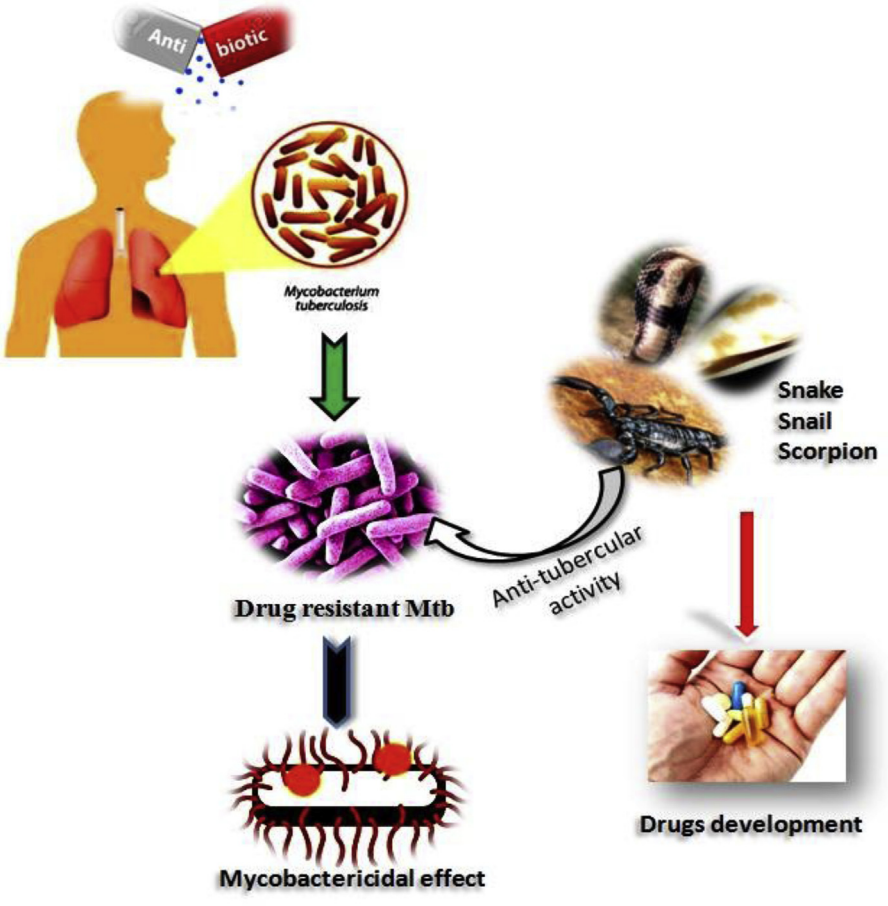


Fig. 4. Plausible development of anti-tubercular drugs from venoms of snakes, snails, and scorpions.

[112]. An oxidized derivative of the α-toxin extracted from *Naja siamensis* venom showed the inhibition of lymphocytes through the chemokine receptors CCR5 and CXCR4 [109,113].

4.2. Scorpion venoms

In scorpion venoms, disulfide-bridged peptides (DBPs) and non-disulfide-bridged peptides (NDBPs) are two major groups of bioactive peptides [114]. The molecular mimicry of lentivirus host cell CD^{4+} receptor causes the binding of few DBPs to HIV gp120 glycoprotein, thereby abolishing the gp120-CD4 interaction, which is important to initialize the alteration in viral envelope that causes viral entry into the host [115]. These CD4 mimetic scorpion toxins constitute approximately 30 amino acid residues, with three or four disulfide bridges, characterized by the cysteine-stabilized α/β motif (CS-α/β), in which a β-turn between the two β-strands in these peptides resembles the CDR2 loop of CD4. *Leiurus quinquestriatus hebraeus* venom associated Charybdotoxin (ChTx) and scyllatoxin present the cysteine-stabilized α/β (CS-α/β) motif and block K^+ channels [116,117].

Peptides and derivatives from scorpion venom were investigated to assess anti-HIV properties. After screening process, peptide derivative Kn2-7 was identified as the promising anti-HIV-1 candidate. Additionally, this peptide revealed low toxicity to host cells with a selective index (SI) of 13.93. Kn2-7 could inhibit all members of a standard reference panel of HIV-1 subtype B pseudotyped virus (PV) with CCR5-tropic and CXCR4-tropic NL4-3 PV strain. Furthermore, it also inhibited a CXCR4-tropic replication-competent strain of HIV-1 subtype B virus. The correlation of anti-HIV-1 property with direct interaction with Kn2-7 and HIV-1 envelope was confirmed using binding assay of Kn2-7 to HIV-1 PV by Octet Red system. The study showed the pronounced anti-HIV-1 role of peptide Kn2-7, and thus, suggested development of anti-HIV-1 drugs in future [118].

4.3. Other venoms

Modified peptides, such as caerin 1.1, caerin 1.9, and maculatin 1.1 isolated from the skin of the amphibians *Litoria caerulea*, *L. chloris*, and *L. genimaculata*, respectively exhibited anti-HIV activity by disintegrating the viral envelope, preventing the virus attachment to cell membrane, and obstructing the viral transfection from dendritic cells to T cells [119]. Bee venom associated PA2 showed anti-HIV property by blocking M and T-tropic HIV virions replication [120]. Fenard et al. [121] showed anti-HIV activity of sPLA2 isolated from bee and snake venoms. In another study, Fenard et al. [122] used bee venom sPLA2 (bvPLA2) associated synthetic peptides as anti-HIV agents. Among them, the p3bv peptide inhibited the replication of T-lymphotropic (T-tropic) HIV-1 isolates, without affecting the monocytotropic (M-tropic) HIV-1 isolates. The peptide also prevented the cell-cell fusion process mediated by T-tropic HIV-1 envelope. Finally, p3bv can block the binding of radio-labeled stromal cell derived factor (SDF)-1a, the natural ligand of CXCR4, and the binding of 12G5. Melittin (an amphipathic peptide) was isolated from *Apis mellifera* venom. It was conjugated with nanoparticles and revealed anti-HIV activity in epithelial vaginal cell line (VK2) and TZM-bl reporter cells [123]. Cecropins peptide is present in several insects other than the hemolymph of infected pupae of the silk moth (*Hyalophora cecropia*). Synthetic hybrid peptide, particularly cecropin A (1–8)-magainin 2 (1–12) showed promising antiviral property by blocking the fusion of virus with host cells [124].

Sea organisms are considered as pivotal sources of antiviral components. Unlike terrestrial animals, few sponge species contain unique peptides with atypical amino acids residues revealing antiviral activity [125]. The cyclic depsipeptides mirabamides A-H, isolated from *Siliquaria spongia mirabilis* and *Stelletta clavosa* exhibit antiviral property by blocking the entry of HIV-1 into TZM-bl cells, thereby avoiding the fusion of viral glycoprotein fusion in order to express CD4 and CCR5 HIV cell receptors [126,127]. Homophymine A (a cyclodepsipeptide) isolated from *Homophymia* sp. also showed *in vitro* anti-HIV-1 activity at lower concentrations [128]. Various peptides and depsipeptides such as koshikamides F and H from *T. swinhoei* and *T. cupola* [129]; papuamides A and B, and theopapuamide A from *Theonella* sp. and *T. swinhoei*, respectively [130–132] had been described as anti-HIV agents by inhibiting the entry of virus into T cells. *S. spongia mirabilis* associated Theopapuamide B also blocked the entry of HIV-1 into host cells [133]. Sponges derived several other anti-HIV-1 peptides were also reported, namely callipeltin A from the genus *Callipelta* [134], celebesides A-C from *S. spongia mirabilis* [133], neamphamide A from *Neamphius huxleyi* [135], and microspinosamide from *Sidonops microspinosa* [136].

Marine arthropods associated tachyplesin and polyphemusin (T140) peptides exhibited antiviral activity by showing attachment to CXCR4. Tachyplesin (17–18 amino acid residues) and polyphemusin (14 amino acid residues) are abundantly present in the horseshoe crabs (*Tachypleus tridentatus* and *Limulus polyphemus*) hemocytes [137,138].

5. Concluding remarks and future perspectives

Venoms are fruitful natural sources of diverse bioactive components which have been exploited as pronounced therapeutic agents against cancer, TB, and HIV infection. In fact, venom constituents possess unique properties such as low-molecular mass, stability, and high potency. Animal's venoms are known to exhibit therapeutic role by diversified mechanisms of action which makes them unexampled agents in a comparison with existing commercial drugs. In recent years, extensive proteomics and genomics approaches have made possible to isolate novel therapeutic components from venoms. Several research activities are focusing combining spectrometric analysis with next generation RNA sequencing to identify novel biologically active peptides exhibiting anticancer, anti-tubercular, and anti-HIV activities. Additionally, nanotechnology has brought entirely new perspectives in the preparations of venom peptide-based drugs. Exploring venom peptides tend to be more beneficial in targeted therapy due to their smaller size and specific target site. Synthetic peptides can undoubtedly be used for eliminating the hurdles of antibodies. Interestingly, currently, few drugs (developed from animal's venom) are in clinical trials phases. Therefore, in the near future, the development of new drugs from animal's venoms might create apparently a new era getting rid of expanding epidemics of cancer, TB, and HIV/AIDS in 21st century.

Conflicts of interest

None declared.

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