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Review

Venoms, toxins and derivatives from the Brazilian fauna: valuable sources for drug discovery

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Abstract: Animal venoms have been widely investigated throughout the world. The great number of biotechnological articles as well as patent applications in the field of drug discovery based on these compounds indicates how important the source is. This review presents a list of the most studied Brazilian venomous animal species and shows the most recent patent applications filed from 2000 to 2013, which comprise Brazilian venoms, toxins and derivatives. We analyze the data according to the species, the type of products claimed and the nationality of the inventors. Fifty-five patent applications were found, involving 8 genera. *Crotalus*, *Lachesis*, *Bothrops* and *Loxosceles* represented 78% of the patent applications. The other 22% were represented by *Phoneutria*, *Tityus*, *Acanthoscurria* and *Phyllomedusa*. Most of the inventions (42%) involved anticancer, immunomodulator or antimicrobial drugs, while 13% involved anti-venoms and vaccines, 11% involved hypotensive compositions, 9% involved antinociceptive and/or anti-inflammatory compositions, and the other 25% involved methods, kits or compositions for various purposes. Brazilian inventors filed 49% of the patent applications, but other countries, mainly the United States of America, Germany, Russia and France, also filed patent applications claiming products comprising venoms, toxins and/or derivatives from the Brazilian fauna. Brazil holds an important number of patent applications which mostly belong to universities and research institutes, but the pharmaceutical industry in this field is still weak in Brazil. Although, Brazilian venomous animal species have been reported in drug discovery throughout the world, many species remain to be explored as valuable and promising tools for drug discovery and development.

Key words: venoms; toxins; patents; Brazilian fauna; drug discovery

源自巴西野生动物的毒液、毒素及其衍生物：药物开发的重要来源

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摘 要：在药物研发领域，野生动物的毒液正被广泛研究，许多基于毒液组分的研究以生物技术应用和专利申请形式被报道。巴西拥有丰富的生物多样性，公布的科研论文和专利申请数量显示了该资源是多么重要。本文报道了一份研究最透彻的巴西有毒动物物种清单及从2000年到2013年的专利申请情况，包括源自巴西有毒物种的毒液成份、毒素及其衍生物。分析了涉及物种的数据、产品类型与发明者的国籍。55个专利申请涉及8个种属，响尾蛇、南美巨蝮蛇、矛头蝮蛇、斜蛛占其中78%。其余22%的专利来自巴西游走蛛、巴西金幽灵蝎、巴西捕鸟蛛、叶水蛙的毒液研究。大多数的发明(42%)包括抗癌、免疫调节剂或抗菌的药物，13%的发明为抗毒血清和疫苗，11%为降压成分，9%为镇痛及抗炎成分，其它25%为一些技术和试剂盒。巴西发明家占专利申请比重的49%，而其它国家如美国、德国、俄罗斯和法国同样发表了巴西动物毒液、毒素

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或衍生物的专利。虽然巴西拥有着大多数有毒物种的专利，但这些专利主要属于其学校和研究机构，药物工业在这方面依然薄弱。迄今为止，在世界范围内，已将巴西的有毒物种运用于药物研发，但大多数的物种可否作为研发的重要工具，仍然需要作进一步的勘探。

关键词：专利申请；有毒物种；毒液；毒素；药物研发
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1 Background

The number of patent applications involving products developed from animal venoms and toxins is huge throughout the world. A simple search at the World Intellectual Property Organization (WIPO) databank (http://patentscope.wipo.int/, accessed in January, 2015) led to 1 608 patent applications containing the word "venom" in the abstract, published from March 1975 to December 2014. Those patent applications were mainly classified with the International Patent Classification (IPC) code A61K, which refers to "human necessities; medical or veterinary science; hygiene preparations for medical, dental, or toilet purposes". The countries with more patent applications in this field, according to the search at WIPO, are China and the United States of America. Accordingly, a simple search at the European Patent Office (EPO) databank (http://worldwide.espacenet.com, accessed in January 2015), using the keyword "venom" in title or abstract, showed 1 897 results. The patent applications involve spider toxins (e.g. CN102205113 – Jingzhaotoxin, from Chinese tarantula *Chilobrachys jingzhao*, claimed for the treatment of apoplexy; WO2011117685 – peptide toxin from Argentinian *Latrodectus mirabilis*, with contraceptive properties; MX2011010576 – peptide toxin from Mexican *Brachypelma verdezy*, with analgesic activity), snake toxins (e.g. EP2708235 – protease inhibitors from African *Dendroaspis angusticeps,* with vasopressin-2 receptor antagonist activity; CN103184207 – streptokinase from Chinese *Agkistrodon acutus*, as a potential antithrombus drug; US2011034386 – natriuretic peptide, from African *Dendroaspis viridis*, claimed for cancer treatment), centipede toxins (e.g. CN101899095 – anti-tumor toxin); toad toxins (e.g. CN102106904 – pharmaceutical preparation to treat palpitation and cardiodynia); bee toxins (e.g. KR20110091997 – serine protease isolated from *Bombus ignitus*, for the treatment of thrombosis); and scorpion toxins (e.g. MX2011005274 – antibiotic peptide from Mexican *Centruroides suffusus suffusus*; CN102399279 – a cell proliferating peptide, from Chinese *Buthus martensii Karsch*), among others.

The huge biodiversity in Brazil puts it on a privileged position for the development of biotechnological products. Brazil is estimated to possess 22% of all animal and plant species on the planet [1].

Rates and colleagues (2011) [2] published a review of the state of the art on molecules and venoms from Brazilian arachnids of medical importance that can be applied in biotechnology. The special focus was on toxins isolated from the scorpion *Tityus serrulatus* and the spiders *Phoneutria nigriventer* and *Lycosa erythrognatha*. They remarked on anti-hypertensive, analgesic, neuroprotective and antimicrobial molecules, as well as molecules that modulate the erectile function. Vetter and colleagues (2011) [3] reported cases of venom-based drug discovery, showing examples of molecules isolated from Brazilian species, such as *Bothrops jararaca* and *Phoneutria sp*. Nunes and colleagues (2013) [4] showed that the use of animal venoms and toxins as pharmacological tools, besides helping the elucidation of the mechanisms involved in a disease, also represents a possible model for new drugs. Altogether, these data show the potential of molecules isolated from Brazilian animal venoms in the development of drugs with various applications.

The present review intends to list the Brazilian venomous animal species that have been studied throughout the years and to show what kind of inventions have already been protected as industrial property on drug discovery, based on the venom of these animals.

2 Venomous animal species found in Brazil

After a search using the key words "Brazilian" and "venom" at PubMed database (http://www.ncbi.nlm.nih.gov/pubmed), performed in January 2015, we found 312 scientific articles, dated from 1955 to 2015. The analysis of these articles enabled us to produce a list (Table 1) of Brazilian species whose venoms have been studied. To this list, we added other species after a

Table 1. Brazilian venomous animal species found in scientific articles and patent databases dated from 1955 to 2015

Groups	Species
Moths and Wasps	*Cerodirphia speciosa, Polybia ignobilis, P. paulista, Protonectarina sylveirae*
Spiders	*Acanthoscurria brocklehursti, A. geniculata, A. gomesiana, A. natalensis, Ctenus medius Keyserling, Phoneutria nigriventer, P. reidyi, Lasiodora sp., Lycosa erythrognatha, Loxosceles adelaida, L. gaucho, L. intermedia, L. laeta, L.similis, Nephilengys cruentata, Avicularia juruensis, Parawixia bistriata, Vitalius dubius*
Cnidaria	*Olindias sambaquiensis, Tamoya haplonema, Chiropsalmus quadrumanus, Physalis physalis, Anemonia erythraea, Bunodosoma caissarum, Stichodactyla duerdeni*
Snakes	*Bothrops alternatus, B. atrox, B.cotiara, B. erythromelas, B. fonsecai, B. insularis, B. jararaca, B. jararacussu, B. moojeni, Crotalus durissus cascavella, C. d. durissus, C. d. terrificus, C. d. ruruima, Lachesis muta muta, L. m. rhombeata, L. trigonocephalus, Micrurus altirostris, M. corallines, M. frontalis, M. lemniscatus, Oxyrhopus trigeminus, Philodryas olfersii*
Conidia	*Conus regius*
Scorpions	*Opisthacanthus cayaporum, Rhopalurus agamemnon, R. Thorell, R. debilis, Tityus bahiensis, T. cambridgei, T. costatus Karsch, T. fasciolatus, T. obscurus, T. serrulatus, T. stigmurus*
Fish	*Cathorops spixii, Potamotrygon cf. Scobina, P. gr. Orbigyni, Scorpaena brasiliensis Cuvier*, *S. plumieri Bloch*, *Thalassophryne nattereri*
Centipedes	*Cryptops iheringi, Otostigmus pradoi, Scolopendra viridicornis, S. angulata*
Frogs and toads	*Brachycephalus ephippium, Bufo rubescens, Epipedobates flavopictus, Phyllomedusa hypochondrialis, Phasmahyla jandaia*

search for patent applications described below. Table 1 lists a total of 42 genera and 78 Brazilian animal species that have their venoms, toxins and derivatives being studied throughout the world since 1955. It is worth mentioning that many genera and species found in Brazil can also be found in adjacent countries, especially those in the Amazon rainforest boundaries.

3 Mapping the patent applications involving products developed from the exploitation of venoms and toxins from the Brazilian fauna

We performed a search at WIPO databank (http://patentscope.wipo.int/search), EPO databank (http://worldwide.espacenet.com) and the Brazilian "National Institute of Industrial Property" (INPI) databank (http://patentesonline.com.br). WIPO databank covers worldwide patent documents and published international patent applications from 42 countries (http://patentscope.wipo.int/search/en/help/data_coverage.jsf, accessed in May 2015); EPO databank manages 92 worldwide patent databases (http://documents.epo.org/projects/babylon/eponet.nsf/0/2464E1CD907399E0C12572-D50031B5DD/$File/global_patent_data_coverage_0711.pdf, accessed in March 2014), while INPI databank contains the patent applications filed in Brazil. For the search, we used the key words "venom", "toxin", "Brazilian", "Brazil" and the 42 genera listed in Table 1, as well as the IPC code A61K, which includes preparations for medical, dental or toilet purposes. These searches were performed between August 2012 and January 2015 and only patent applications filed after the year 2000 were considered. The year 2000 corresponds to the date from which INPI, through the resolution 207/09 (http://www.wipo.int/wipolex/en/text.jsp?file_id=205616, accessed in December 2013), normalized the procedures related to the requirement of patent applications of inventions that have been developed with an access to samples of components of the national genetic resource. According to article 2 of this resolution, the patent applications comprising access to the national genetic resource, performed after June 2000, should include a specific form, where the origin of the genetic material, as well as the number of the corresponding authorization of access, should be informed. This resolution is in accordance with what was stated in the Convention on Biological Diversity (http://www.wipo.int/wipolex/en/other_treaties/text.jsp?file_id=184778, accessed in December 2013) and to what was ruled in Brazil through the Provisional Law number 2.186-16 (http://www.wipo.int/wipolex/en/text.jsp?file_id=225641, accessed in December 2013).

Through this search, we found 55 different patents or

patent applications, filed from 2000 to 2013. The application number, the priority date, the applicants, the nationality of the inventors, the Brazilian species involved and the type of invention are listed in Table 2. Table 2 shows that, out of the 42 genera investigated, only 8 (19%) were involved in intellectual properties (Fig. 1).

Crotalus, claimed in 14 patent applications, is the most investigated Brazilian genus for drug discovery. The patent applications involving *Crotalus* (rattlesnakes) claimed a variety of products: antimicrobial drugs, drugs for cancer treatment, analgesic drugs, drugs to treat AIDS, drugs for the treatment of strabismus, blepharospasms and nystagmus, anti-inflammatory agents and others. Kerkis and colleagues (2014) [5] recently reviewed the natural cell penetrating and antimicrobial peptide (CPP and AMP) from *Crotalus*, named crotamine, which has a wide spectrum of biological activities, from antimicrobial to anticancer, with potential biotechnological and therapeutic uses. They showed that crotamine has a positively charged N-terminal domain that enables its interaction with negatively charged cell membranes, such as microbial membranes and cancer cell membranes, which are more negative than normal cells. Crotamine also interacts with secondary targets, interrupting vital metabolic processes. In addition, it selectively blocks mammalian voltage-gated potassium channels. The same authors show that synthetic peptides derived from crotamine are a promising path for drug development.

Lachesis (South American bushmaster) and *Bothrops* (lancehead snakes) ranked on the second and third places, with 12 and 11 patent applications, respectively. *Lachesis* venoms and toxins are claimed in anti-ageing and antioxidant preparations, antimicrobial formulations, immunomodulators, formulations for reabsorption and prophylaxis of hemorrhage in vascular ophthalmic diseases, among others. Da Silva Cunha and coworkers (2011) [6] showed that a phospholipase A_2 from the venom of *Lachesis muta* increases the survival of axotomized rat retinal ganglion cells, through the generation of lysophosphatidylcholine, showing a possible role of this enzyme in controlling the survival of axotomized neuronal cells.

Bothrops venoms and toxins are claimed in hypotensive and vasodilator formulations, drugs for the treatment of chronic degenerative diseases, modulators of acetylcholine receptors, anticoagulant and thrombolytic formulations, bactericides and others. The bothropic structure of acidic PLA_2 (BthA-I, from *B. jararacussu* venom; $BmooPLA_2$-I from *B. moojeni*) have been shown to exhibit inhibitory effects on platelet aggregation, blood pressure decrease, and bactericidal effects [7]. A patent application from the United States of America, granted in 1977 (U.S. Patent 4,046,889), claimed the use of an angiotensin-converting enzyme inhibitor (captopril). This molecule was developed based on studies with the venom of the Brazilian viper *Bothrops jararaca* [8], and has been on the market since 1981, for the treatment of hypertension and some types of congestive heart failure [9].

Following the snakes, two spider genera rank on the fourth and fifth places: *Loxosceles* (brown or recluse spiders) and *Phoneutria* (armed spider), respectively. *Loxosceles* venoms and derivatives are involved in inventions that mainly claim formulations for cancer

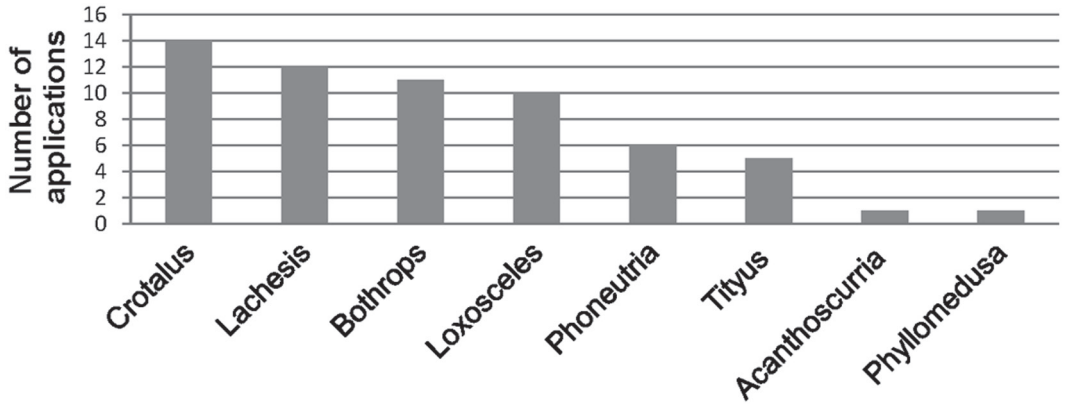

Fig. 1. Number of patent applications by genus involving products developed from the exploitation of venoms and toxins from the Brazilian fauna.

Table 2. Patent applications filed after the year 2000 comprising the use of information from Brazilian animal venoms, toxins and/or derivatives, available at WIPO, EPO and/or INPI

	Application number	Priority date (DD-MM-YYYY)	Also filed as	Applicants	Nationality of the inventors	Brazilian species involved	Type of invention
1.	DE20001024383 WO2001EP05670	17-05-2000 17-05-2001	WO0187346, JP2003533203, EP1283726, AU6229701	WEICKMANN DIRK	Germany	*Loxosceles laeta*	Treatment of mucosa and skin tumor
2.	BR20000001870	29-05-2000	WO0192290, US2006276380, US7723468, US2003186854, AU6367601	USP CNRS	Brazil and France	*Acanthoscurria gomesiana*	Antiparasitic, fungicide and bactericide
3.	BR20010001088	19-03-2001	WO2002074782, US2005031604, JP2005505245, EP1587819, CA2440749	Biolab Sanus Farmacêutica Ltda	Brazil	*Bothrops jararaca*	Hypotensive and vasodilator
4.	AR2001P101891 AR2001P105751 WO2002ES00198	24-04-2001 11-12-2001 24-04-2002	WO02085391, EP1391207, US2007184046, US2004166104	Luis Alberto Costa	Argentina and Spain	*Crotalus durissus terrificus*	Treatment of viral, bacterial or parasitic infections
5.	BR20010104510	27-07-2001	US2004242488, MXPA04000806, JP2005508878, EP1412380, CA2453112 , O03010191, AU2002317638, AR036192	EMBRAPA; UNB	Brazil	*Phyllomedusa hypochondrialis*	Antimicrobial peptide
6.	RU20010122763	13-08-2001	-	Nebera Sergej Anatol'evich	Russia	*Lachesis*	Anti-ageing antioxidant preparation
7.	BR20020205774	27-02-2002	WO03072132, AU2003209869	FUNED; FAPEMIG	Brazil	*Bothrops jararaca*	Adjuvant for the production of antibodies and vaccines
8.	RU20020111635	06-05-2002	-	Romanov Vladimir Vladimirovich	Russia	*Lachesis*	Prevention and treatment of viral and bacterial infections in avian
9.	BR20020002157	07-06-2002	WO2003104274, US2007275901, US2006014928, US7192925, EP1534743, EP1534743, BR0202157, AU2003229155, AT417061	UFMG	Brazil and France	*Tityus serrulatus*	Hypotensive
10.	BR20020202596	27-06-2002	-	UFMG	Brazil	*Loxosceles intermedia*	Anti-venom and vaccine
11.	BR20020204051	01-10-2002	-	Roberto Piraino	Brazil	*Lachesis muta*	Immunomodulator
12.	FR20020014490	19-11-2002	KR101172700, US2004096925, JP2012224637, JP2009108104, JP2004166684, FR2847267, DE10362194, DE10320603, CH694107	COLETICA	France	*Crotalus durissus*	Method to test PLA2 inhibitors
13.	US20020306958 US20060336630 US2006240117	02-12-2002 20-01-2006	-	LECCA PEDRO J	USA	*Crotalus durissus*	Cancer treatment
14.	BR20020005449	09-12-2002	WO2004052273, US2008199503, MXPA05006170, JP2006517520, EP1581550, CN1820018, CA2507980, AU2003302871	Biolab Sanus farmacêutica	Brazil	*Bothrops jararaca*	Treatment of chronic degenerative diseases
15.	RU20030102092	27-01-2003		DAVYDENKOV VALERIJ NIKOLAEVICH	Russia	*Lachesis mutus*	Treatment and prevention of chronic or acute sepsis
16.	BR20030301513	16-05-2003	WO2004100860	FAPESP	Brazil	*Bothrops, Crotalus durissus terrificus*	Hyperimune serum
17.	DE20031022656	20-05-2003	-	TOXIMED GMBH; WEICKMANN, DIRK	Germany	*Crotalus durissus terrificus*	Treatment of renal tumor

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18.	RU20030116638	04-06-2003	-	NEBERA O.A; NEBERA S.A	Russia	*Lachesis*	Reabsorption and prophylaxis of hemorrhage in vascular ophthalmic diseases
19.	DE20031057970	11-12-2003	WO2005056027, EP1699473	TOXIMED GMBH; WEICKMANN, DIRK	Germany	*Loxosceles laeta; L. gaucho*	Organic solvent
20.	BR2004PI00192	11-02-2004	WO2005081613	Biolab Sanus Farmacêutica	Brazil	*Bothrops jararaca*	Modulators of acetylcholine receptors
21.	DE200410008417	20-02-2004	-	TOXIMED GMBH	Germany	*Crotalus durissus durissus*	Treatment of liver, colon and renal cancer
22.	DE200410019323	21-04-2004	WO2005103231	TOXIMED GMBH	Germany	*Loxosceles*	Treatment of renal cancer
23.	BR2004PI01702 BR2005PI02399 WO2005BR00073	06-05-2004 02-05-2005 06-05-2005	WO2005107357, US2009203618, PT1765851, JP2008504234, ES2377635, EP1765851, CN101048170, CA2565731, AU2005239771, AT533776	Laboratório Biosintética Ltda	Brazil	*Crotalus durissus terrificus*	Analgesic peptides
24.	US20040917143	13-08-2004	-	REID PAUL; QIN ZHENG H	USA	*Crotalus durissus terrificus*	Treatment of chronic pain
25.	MX2004PA08435 WO2005MX00071	31-08-2004 29-08-2005	US8287860,WO2006025718, BRPI0514809, AU2005280742, AR055482	UNIVERSIDAD NACIONAL AUTONOMA DE MEXICO; LABORATORIOS SILANES S.A. DE C.V	Mexico	*Loxosceles laeta*	Immunogens and anti-venoms
26.	US20040934594	02-09-2004	-	REID PAUL F	USA	*Crotalus durissus terrificus*	Treatment of AIDS
27.	BR2004PI04765	03-11-2004	-	FUNDACAO BUTANTAN	Brazil	*Loxosceles intermedia*	Process for the production of equine anti-loxoscelic serum
28.	BR2004PI06273	23-12-2004	-	FAPEMIG; UFU	Brazil	*Bothrops moojeni*	Anticoagulant and thrombolytic enzyme
29.	DE200510011111	10-03-2005	-	TOXIMED GMBH	Germany	*Loxosceles laeta; L. gaucho*	Tumor treatment
30.	BR2005PI01233	04-04-2005	-	UFSCAR; FAPESP; UERJ	Brazil	*Bothrops alternatus*	Induction and suppression of neovascularization
31.	US20050674342P	22-04-2005	WO2006116156, BRPI0607750, NZ562201, NO20076013, MX2007013031, KR20080021606, JP2008538506, EP1896080, EA200702313 CR9452, CA2604999, AU2006239928 AR053234 (A1)	AMGEN INC	USA	*Tityus serrulatus*	Treatment of auto-immune diseases
32.	BR2005PI02080	02-06-2005	-	FUNDACAO BUTANTAN	Brazil	*Lachesis muta*	Process of production of equine anti-lachesic serum
33.	DE200510027478	14-06-2005	-	TOXIMED GMBH	Germany	*Crotalus durissus terrificus*	Treatment of renal tumor
34.	DE200510027665	15-06-2005	WO2006134166	TOXIMED GMBH	Germany	*Loxosceles gaucho; Loxoceles laeta*	Treatment of brain tumor
35.	US20050721270P	27-09-2005	WO2007038619, JP2009509535, EP1929073, CA2622441, AU2006294644	AMUNIX INC	USA	*Phoneutria*	Biologically active proteins for the treatment of various diseases
36.	US2005073429 US20060594173	08-11-2005 08-11-2006	-	GOPALAKRISHNAKONE PONNAMPALAM; SAMY RAMAR P	Singapore	*Crotalus durissus terrificus, Bothrops jararacuçu*	Bactericide

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37	US20050313377	22-12-2005	-	REID PAUL F	USA	*Crotalus durissus terrificus*	Analgesic
38	CN20061044594	25-05-2006	-	QILU PHARMACEUTICAL CO LTD	China	*Bothrops atrox*	Batroxobin extraction method
39	CN20061047690	08-09-2006	-	SHENYANG SHOUZHENG BIOLOG TECH	China	*Bothrops atrox*	A mixture of Batroxobin and interleukin-11 to stop bleeding
40	BR2006PI05484	21-11-2006	WO2008061329, US2010168009, EP2086558, CA2669975	UFMG	Brazil	*Phoneutria nigriventer*	A 55-aminoacid toxin, Pha-1B, calcium channel blocker, for the treatment of neurologic diseases and pain
41	BR2007PI02089 WO2007BR00306	09-03-2007 08-11-2007	EP2134368, US2010226863	ROBERTO PIRAINO	Brazil	*Lachesis muta*	Immunomodulation homeopathic formulation
42	BR2007PI02734	02-04-2007	-	UFMG	Brazil	*Phoneutria nigriventer*	PhKv toxin, for the treatment of stroke, traumatic head injuries and CNS degenerative diseases
43	US20070916923P US20080118030	09-05-2007 09-05-2008	-	REEVES WILLIAM H; LAGUENS RUBEN P; MARSHECK WILLIAM J; LAGUENS MARTIN	Argentina USA	*Lachesis muta muta*	Formulation containing the venom from *Lachesis* to diminish TNF-alpha for the treatment of sepsis, parasitic infections, nephrotoxicity, rheumatoid arthritis, cancer and AIDS.
44	BR2007PI05590	07-08-2007	WO2009018643	UFMG	Brazil	*Crotalus durissus terrificus*	Crotoxin for the treatment of strabismus, blepharospasms and nystagmus.
45	IE20070000737 WO2008EP08602	10-10-2007 10-10-2008	US2010316737	FARRINGTON, DANIEL; FARRINGTON, THOMAS	Ireland USA	*Lachesis muta*	Anti-microbial agents
46	BR2007PI06261	08-11-2007	-	UFPR	Brazil	*Lachesis*	Homeopathic composition for the positive regulation of antigen presenting cells
47	BR2007PI06234	08-11-2007	-	UFPR	Brazil	*Lachesis*	Homeopathic composition for negative regulation of the multiplication of the virus h5n1
48	BR2008PI00596 WO2009BR00040	31-01-2008 30-01-2009	WO2009094742, EP2247730, CN101981190, AU2009208322	UFMG; FUNED; FAPEMIG	Brazil	*Phoneutria nigriventer*	Tx2-6, for the potentiation of the erectile function
49	BR2008PI01542	18-03-2008	-	UFMG	Brazil	*Tityus serrulatus*	Hypotensive peptides
50	BR2009PI02312	15-07-2009	-	FAPESP; USP	Brazil	*Crotalus durissus terrificus and Tityus serrulatus*	Anti-tumor and anti-inflammatory agents
51	US20090234429P	17-08-2009	WO2011022357 EP2467477 CA2770185	EAST CAROLINA UNIVERSITY	USA	*Tityus serrulatus*	Metalloproteinase for the treatment of various diseases.
52	BR2010PI04449	30-04-2010	-	UFMG; FUNED	Brazil	*Bothrops jararaca*	Kit containing an enzyme extracted from the venom, to test anti-bothropic sera
53	US201113704729	16-06-2011	WO2011158242	FUTURAGENE ISRAEL LTD	Israel	*Phoneutria nigriventer*	Plants resistant against herbicides containing a combination of spider toxin and a chitinase
54	BR102012020800	20-08-2012	WO2013BR00319	UFMG	Brazil	*Phoneutria nigriventer*	Synthetic peptide to treat erectile dysfunction
55	US2015030691	26-07-2013	-	NATURES INNOVATION INC	USA	*Lachesis muta*	Analgesic composition

treatment, while *Phoneutria* is involved in patent applications claiming for formulations to treat neurologic diseases, pain, stroke, traumatic head injuries and central nervous system (CNS) degenerative diseases, as well as for the potentiation of erectile function. The venom of *Phoneutria nigriventer* is rich in toxins that affect voltage-gated sodium, calcium, and potassium channels as well as glutamate transporters [10]. Interestingly, a synthetic peptide derived from a toxin that acts on sodium channels showed erectile effects and no toxicity, enhancing the production of nitric oxide (NO) without interacting with ion channels (unpublished data).

A scorpion, *Tityus serrulatus*, appears on the sixth place, involved in patent applications for hypotensive, anti-tumor, anti-inflammatory agents and others. Verano-Braga and colleagues (2008) [11] described, for the first time, a family of *T. serrulatus* peptides that are similar to bradykinin, potentiating hypotensive effects. They synthesized a smaller peptide that held the same effect, and was able to induce endothelium-dependent vasorelaxation through NO release. Guo and colleagues (2013) [12] described *T. serrulatus* peptides with broad spectrum antimicrobial and anticancer cell activities, which could be improved by increasing their cationicity. These examples show that studies of structure-function of toxins enable the synthesis of molecules with improved specific activities, leading to the development of future drugs that are better directed to target.

The inventions involving the use of Brazilian venoms, toxins and/or derivatives are mostly related to anticancer or antimicrobial drugs (42%), anti-venoms and/or vaccines (13%) and hypotensive compositions (11%), but other classes of drugs are also found, as shown in Table 3.

Table 3. Number of patent applications by type of invention involving products developed from the exploitation of venoms and toxins from the Brazilian fauna

Type of invention	Number of patent applications
Pharmaceutical compositions for the treatment of cancer	12
Antimicrobial or immunomodulator compositions	11
Antibodies, vaccines and sera	7
Anti-hypertensive compositions and/or compositions for the treatment of vascular diseases	6
Antinociceptive and/or anti-inflammatory compositions	5
Methods and kits	3
Compositions for the treatment of degenerative diseases, AIDS and/or other diseases	12
Other inventions	2

4 The origin of patent applications involving venoms from species found in Brazil

Brazil holds the highest number of applications (49%), followed by the USA (16%) and Germany (15%) (Fig. 2).

It is noteworthy that, from all Brazilian applicants, government universities and foundations were the main applicants (70%). The opposite can be observed for the foreign applicants, which had 85% of the applications filed by companies or independent inventors (Fig. 3).

The numbers show that Brazilian researchers are not yet mobilized towards protecting and transferring their technology. Moreira and colleagues (2006) [1] showed that most of the patent applications involving technolo-

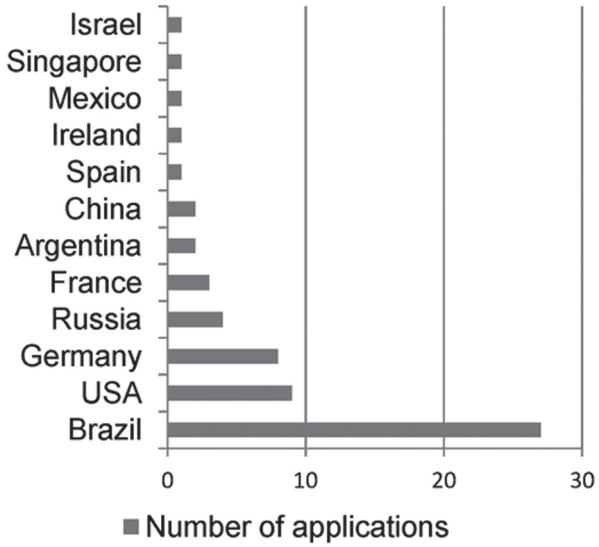

Fig. 2. Number of patents by nationality of the inventors involving products developed from the exploitation of venoms and toxins from the Brazilian fauna.

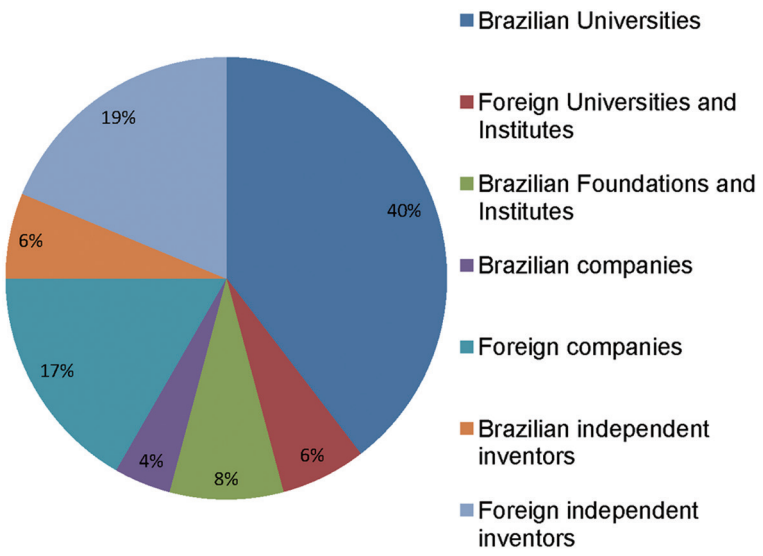

Fig. 3. Percentage of patent applications by type of institution involving products developed from the exploitation of venoms and toxins from the Brazilian fauna.

gies based on Brazilian plants are filed by foreign inventors (approximately 94%, while 6% are filed by Brazilian industries, universities and institutes). According to Taylor Wessing's 4th Global Intellectual Property Index (GIPI) (http://www.taylorwessing.com/ipindex/, accessed in February 2014), Brazil ranked at the 31st position in number of patent applications, in 2013. On the other hand, according to SCImago Journal and Country Rank (http://www.scimagojr.com, accessed in February 2014), Brazil ranked at the 10th place for biotechnology publications in 2012, showing that the scientific production in Brazil is much more active than the protection of new technology. Therefore, public policies and private investments should improve, in order to enhance innovation and technology transfer in Brazil.

5 Conclusions

Despite Brazil's rich biodiversity, only 8 genera of Brazilian venomous animal species were found to be involved in patent applications: *Crotalus*, *Lachesis*, *Bothrops*, *Loxosceles*, *Phoneutria*, *Tityus*, *Acanthoscurria* and *Phyllomedusa*. The inventions are mostly related to anticancer, antimicrobial drugs, anti-venoms and/or vaccines, and hypotensive compositions. Although Brazil holds an important number of patent applications involving venoms from its fauna, they mostly belong to universities and research institutes, showing that the pharmaceutical industry in Brazil is investing little in this field. Brazilian venomous species have been used in drug discovery throughout the world, and some foreign companies have patent applications comprising these venoms, toxins or derivatives. However, a great number of Brazilian venomous species remains to be explored as valuable and promising tools for drug discovery and development.

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