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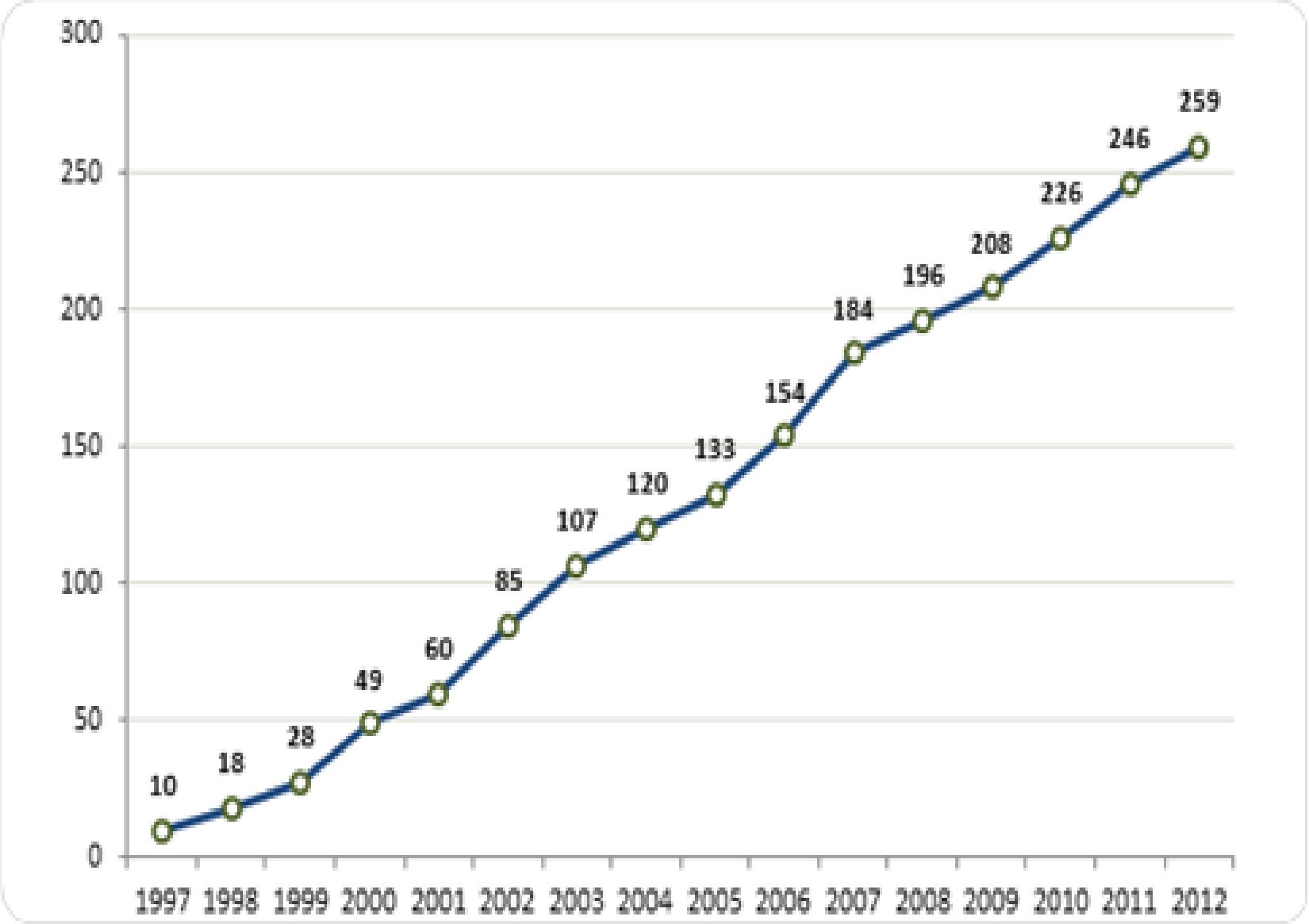

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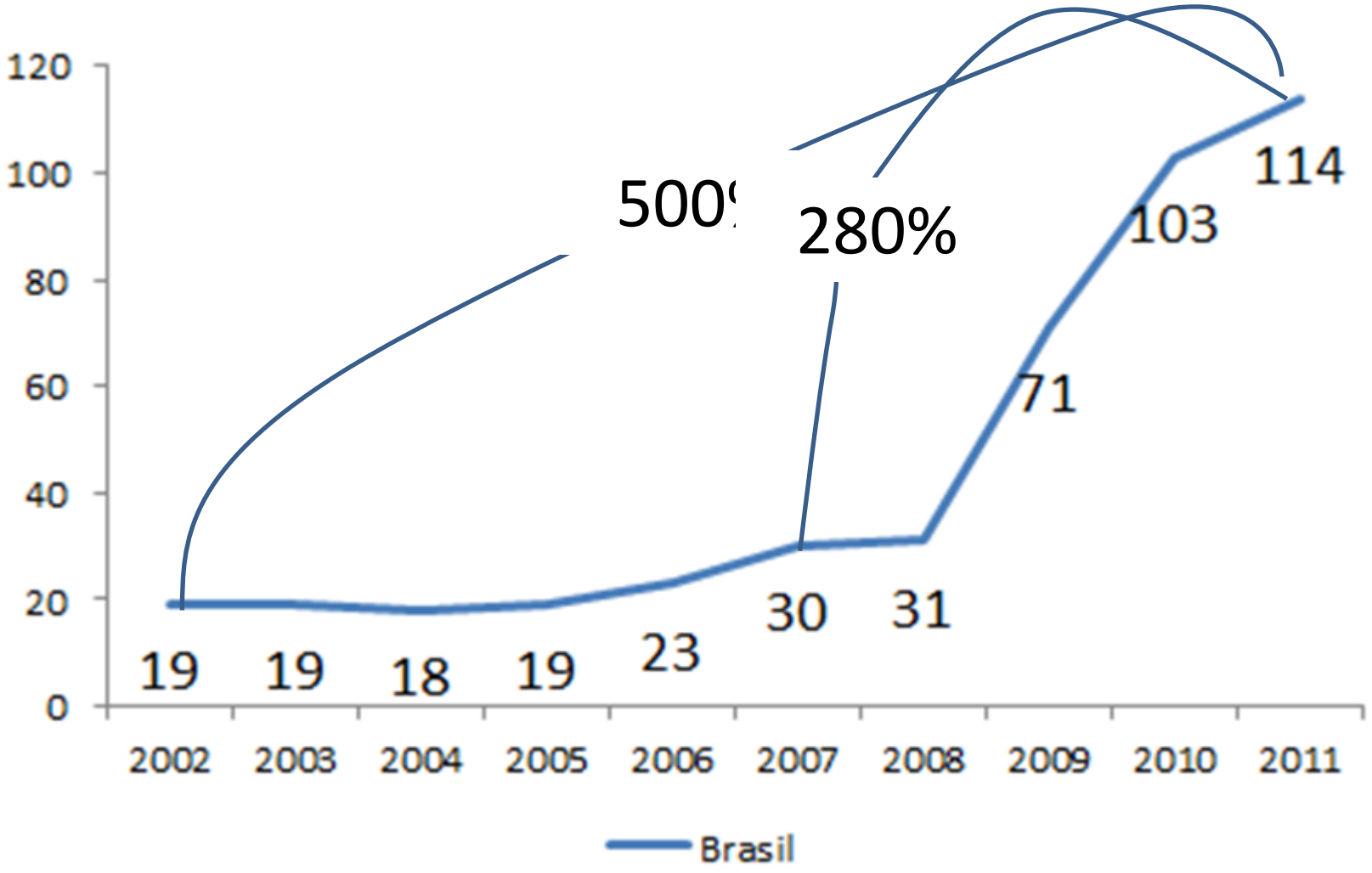

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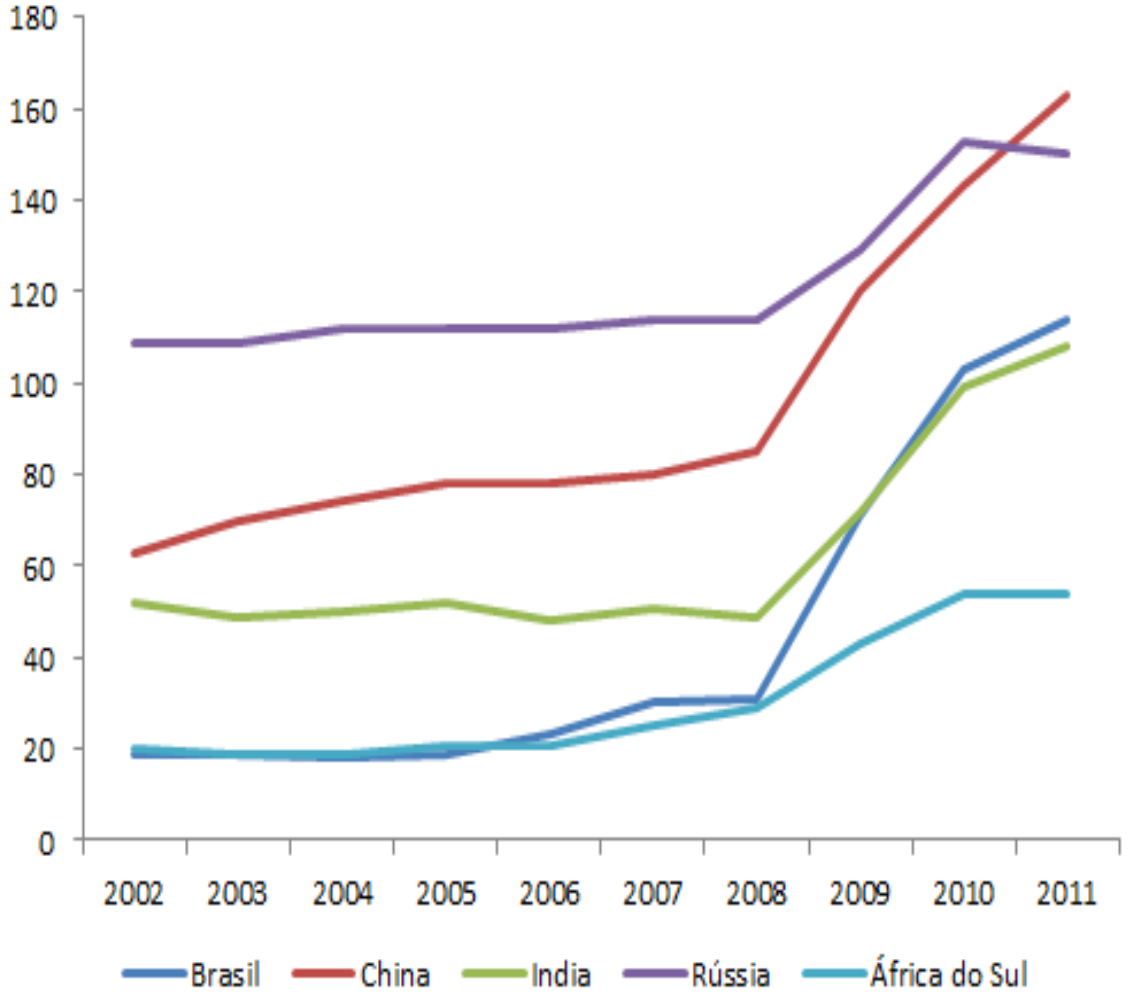

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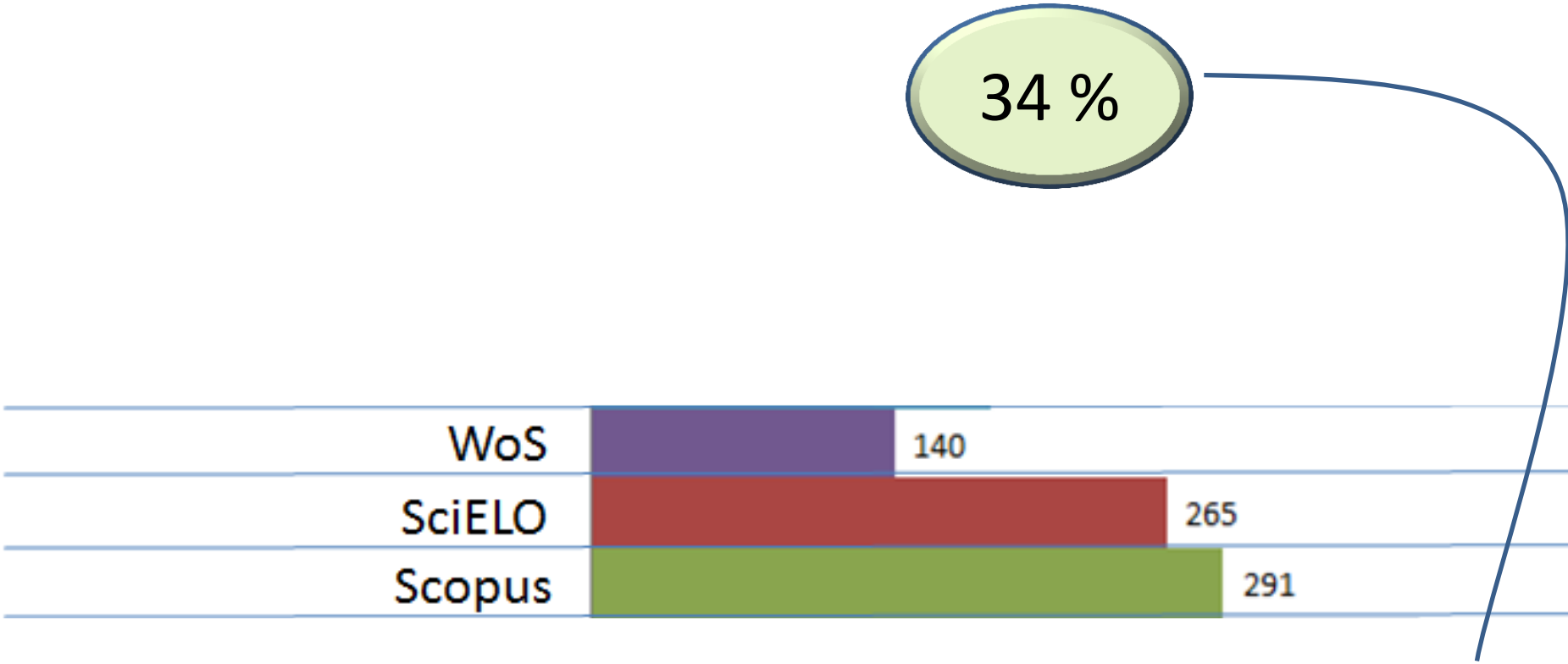

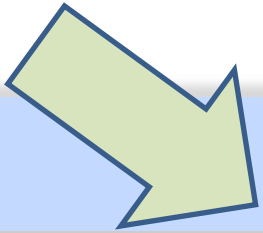

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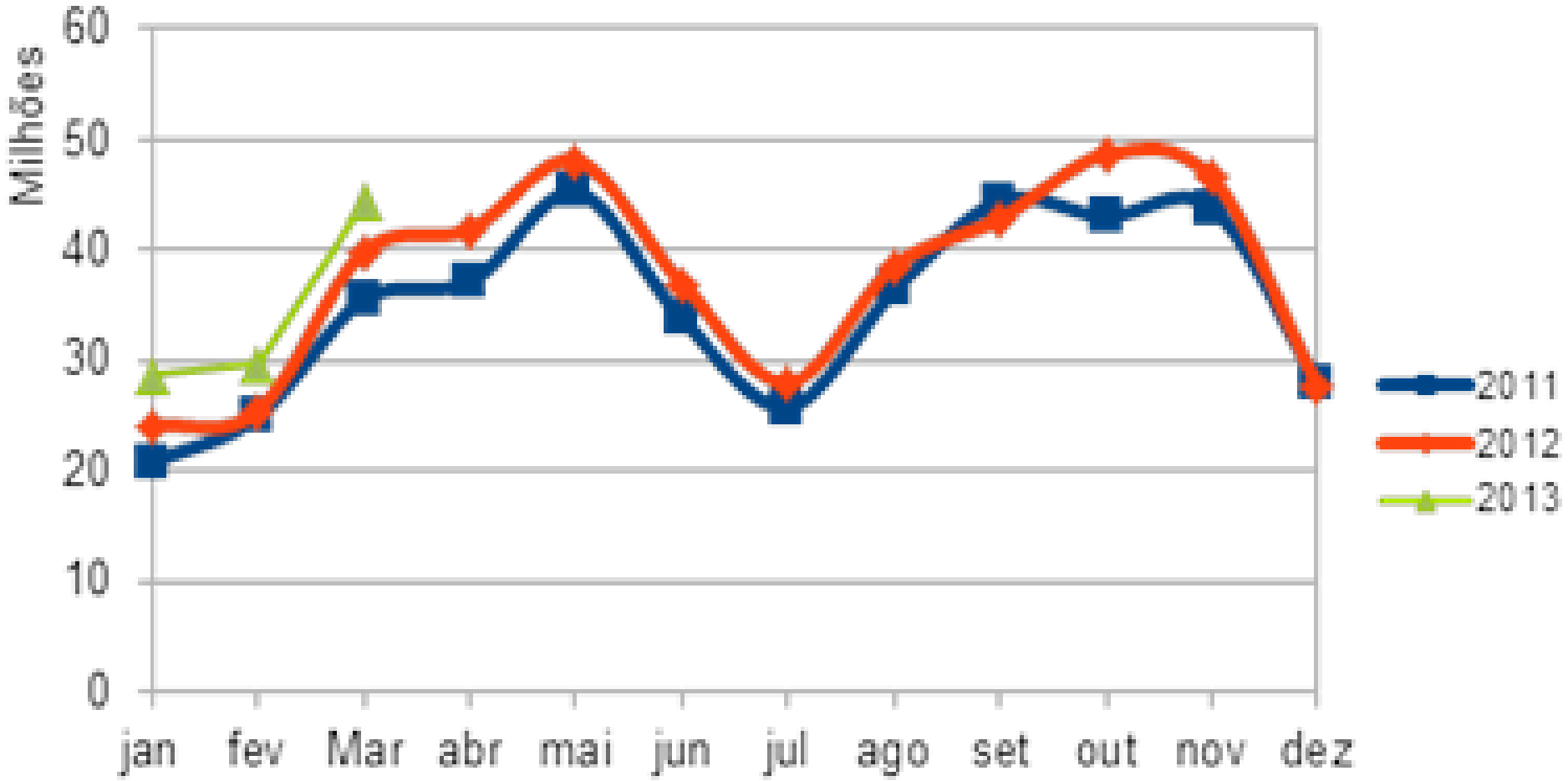

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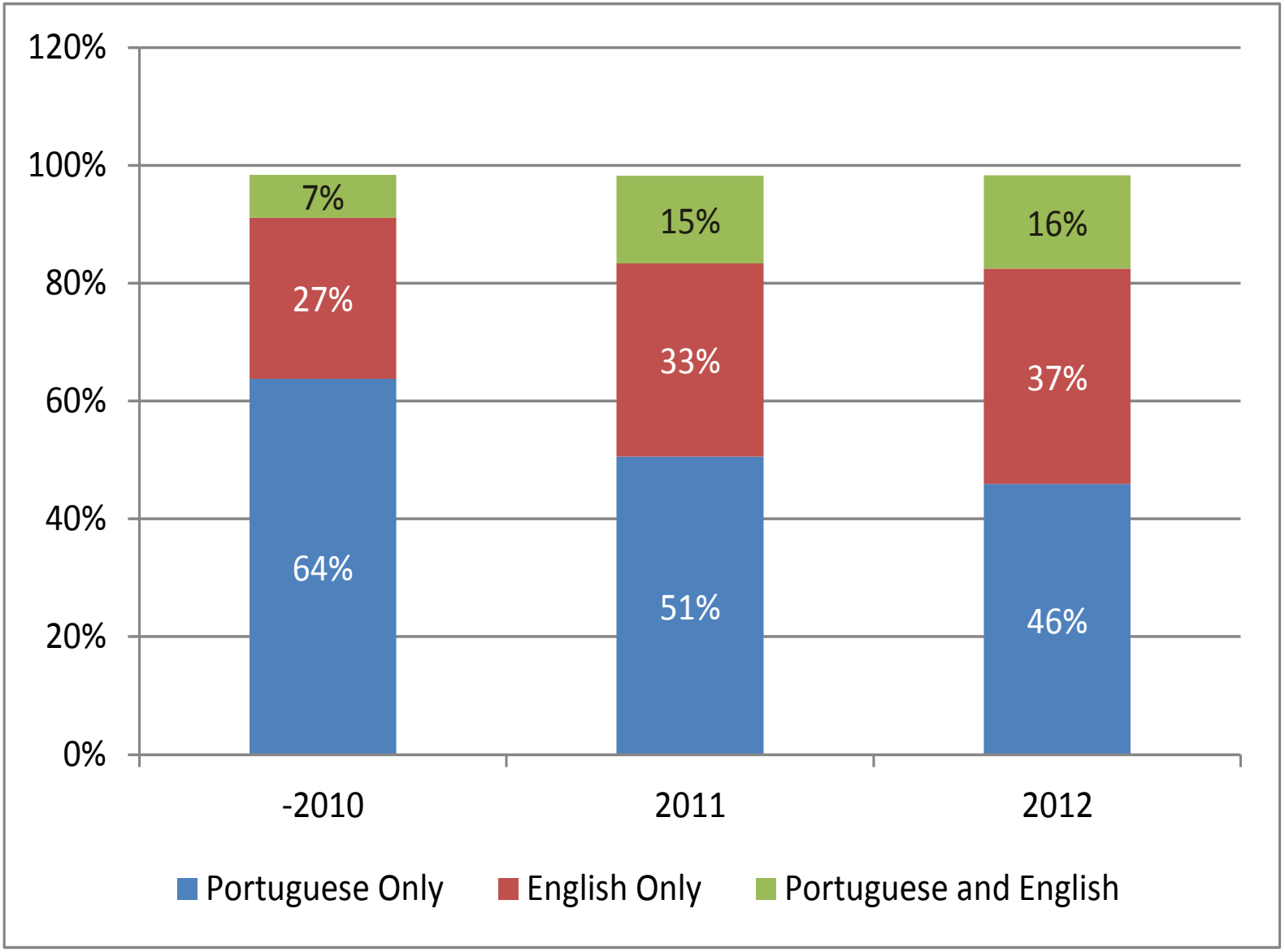

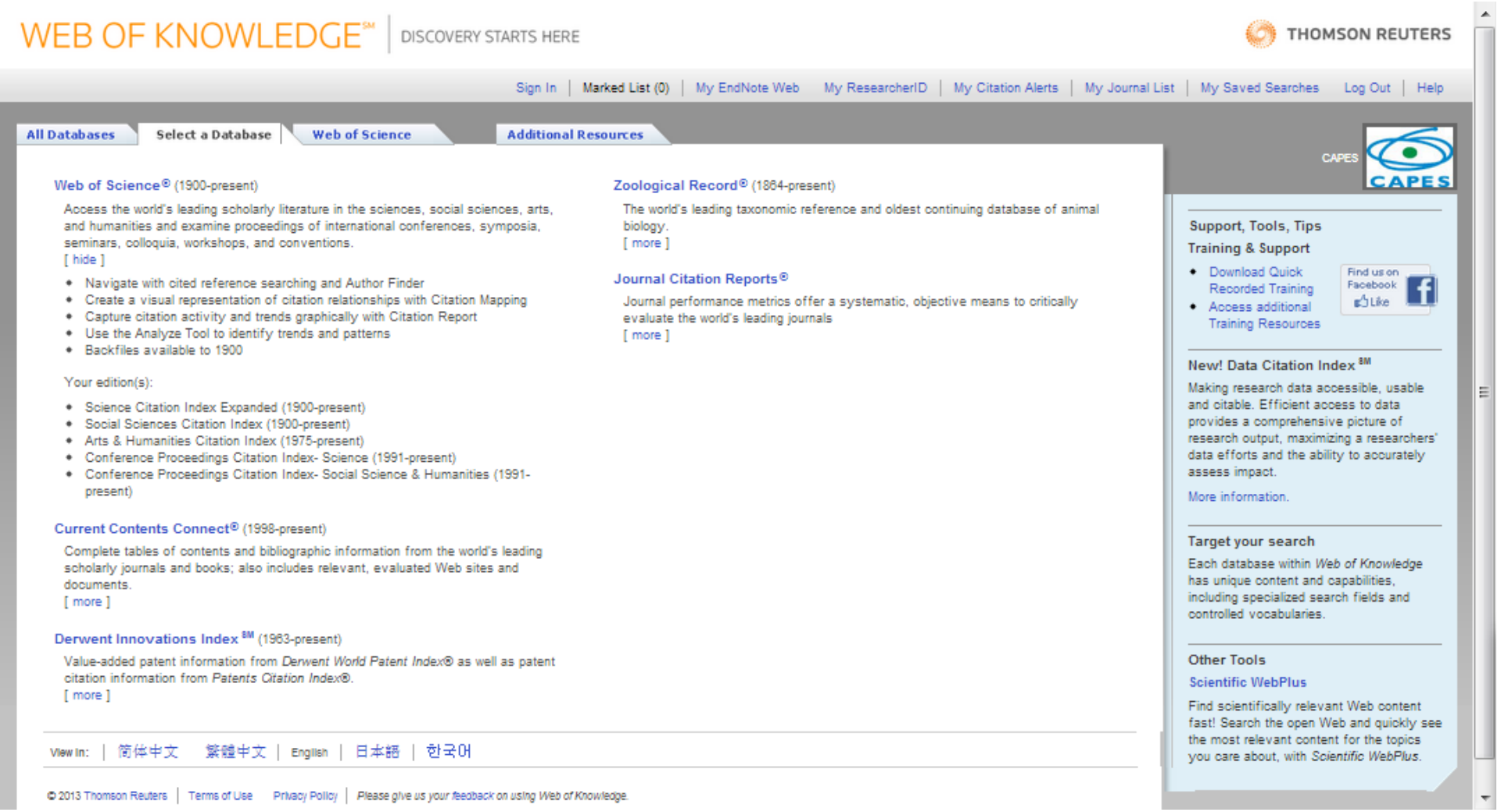

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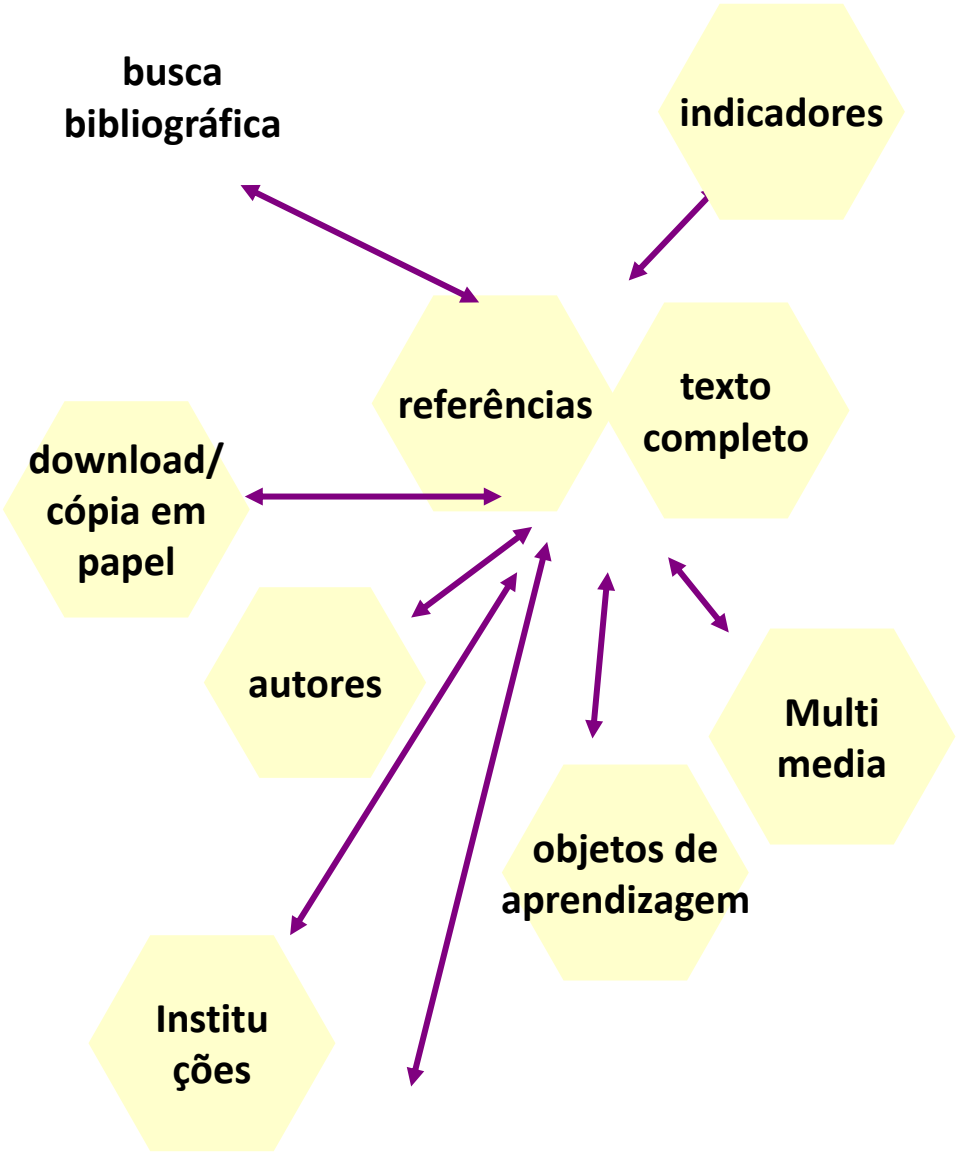
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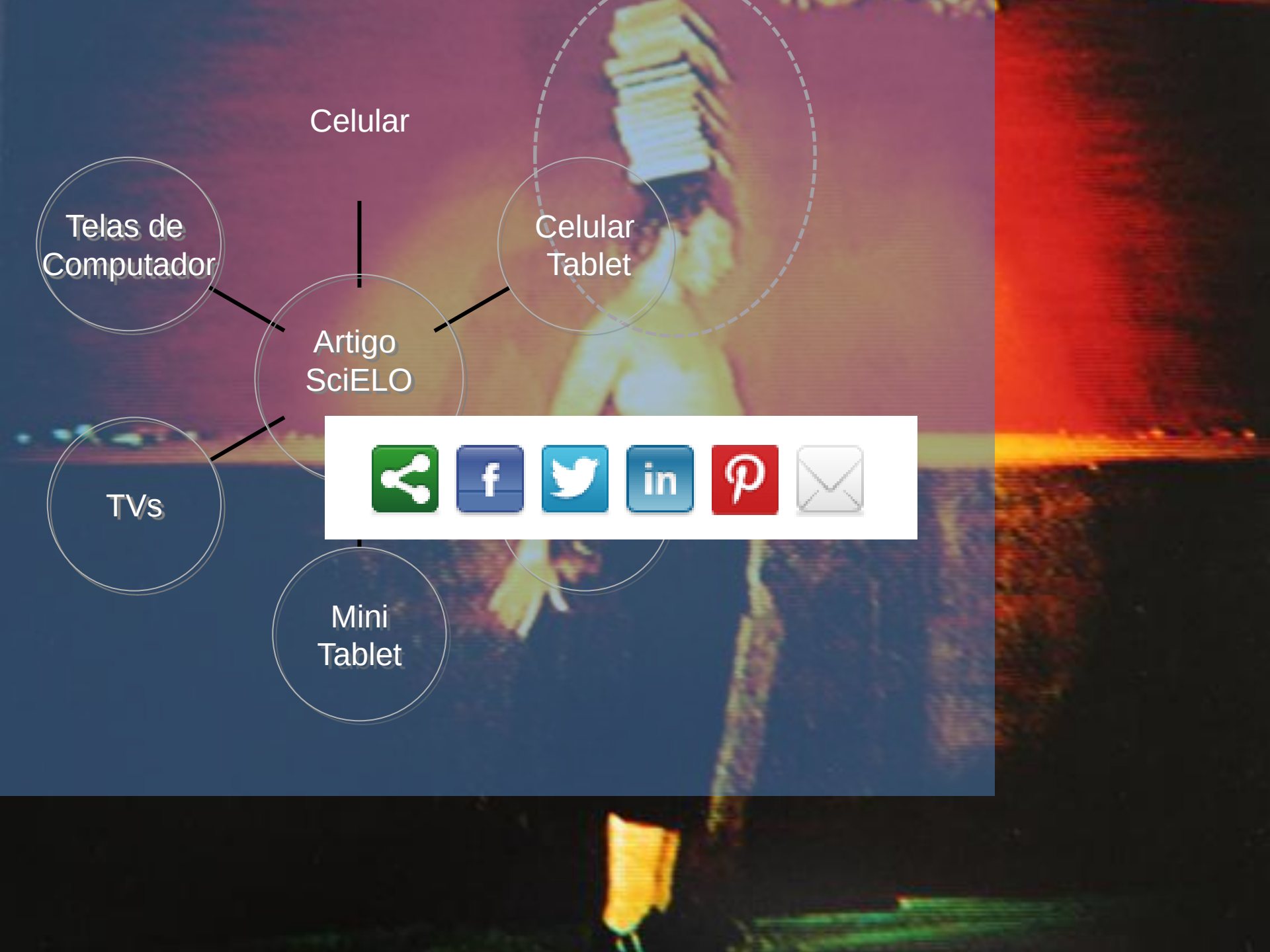
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Abel L. Packer
Programa SciELO / FAPESP, Coordenação
Consultor de informação e comunicação em ciência da FAPUNIFESP

São Paulo, 17 maio 2013

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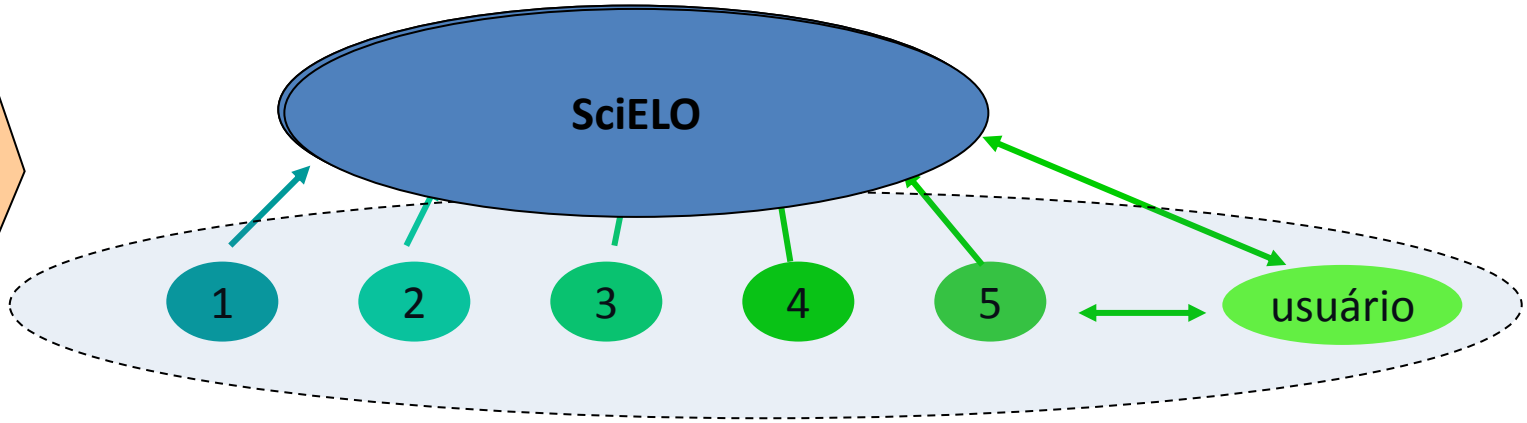

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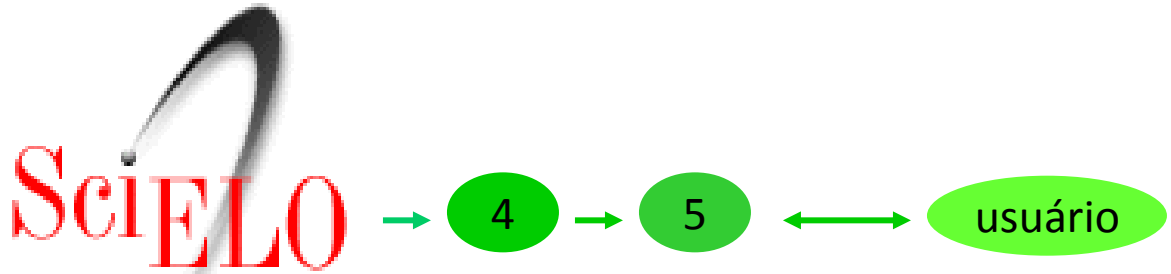

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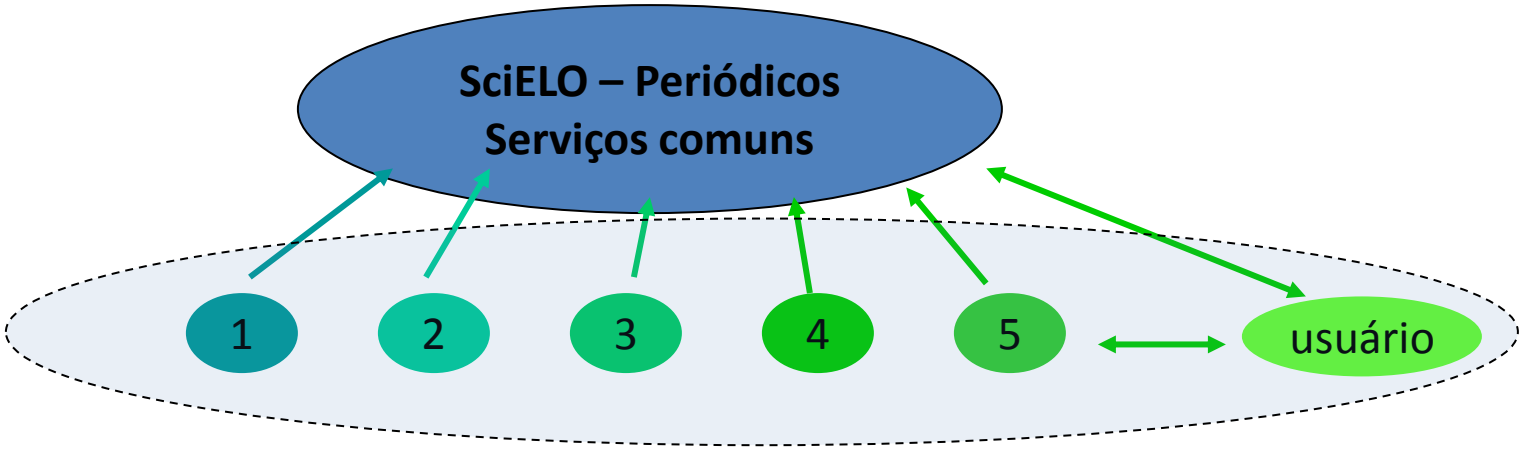

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Biomedical Sciences

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Article Indicators

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Spindola, H.M. [1] Cabral, E. [3] Eberlin, M.N. [3] Tinti, S.V. [3]
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Author affiliation

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Publication dates

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Keywords:
Chromobacterium sp, Antitumor activity, Secondary metabolites, Genetic diversity, Violacein

Introduction

Microorganisms have become an important source of natural products of great interest to pharmaceutical industries. Among current commercially available drugs, approximately 63% are directly or indirectly derived from natural products from microorganisms, plants and animals [1]. *Chromobacterium violaceum* is a Gram-negative β-proteobacterium, facultative anaerobic, saprophyte, free-living soil- and water-associated microorganism, found in tropical and subtropical regions and it is abundant in black waters and on the banks of Rio Negro, in Amazonas, Brazil [2]. The main characteristic of this bacterium is the production of violacein, a purple pigment, which exhibits activity against important tropical pathogens such as *Mycobacterium tuberculosis*, *Trypanosoma cruzi*, *Leishmania* sp, and *Plasmodium* and is reported to have bactericidal, cytotoxic, antiviral, antifungal, antioxidant, antitumor [3], antiulcerogenic, immunomodulatory, analgesic, antipyretic, and anti-diarrheal [4,5] activities. Several studies have shown that violacein is also capable of inducing apoptosis in a variety of cancer cell lines, including leukemia lineages, suggesting a promising clinical application to cancer treatment. The therapeutic application of violacein to cancer chemoprevention has been the focus of recent investigations [6,7]. Violacein has been shown to cause apoptosis in HL60 leukemic cells but is ineffective in normal human lymphocytes and monocytes [8]. In all of the cases observed until now, the toxicity to normal cells requires larger amounts of violacein compared to cancer cells. The IC_{50} for cancer cells is about 1–3 μM, as opposed to about 8–10 μM for normal cells [3].

1 Microbial antitumor drugs: natural products of microbial origin as anticancer agents
Curr Opin Investig Drugs, 2009

2 Genetic characterization of *Chromobacterium* isolates from black water environments in the Brazilian Amazon
Hungria M, Astolfi-Filho S, Chueire LM, Nicolas MF, Santos EB, Bulbol MR.
Lett Appl Microbiol 2005; 41: 17-23, doi: 10.1111/j.1472-765X.2005.01724.x.

3 *Chromobacterium violaceum*: a review of pharmacological and industiral perspectives
Crit Rev Microbiol, 2001

4 Immunomodulatory, analgesic and antipyretic effects of violacein isolated from *Chromobacterium violaceum*
Phytomedicine, 2010

5 Anti-diarrhoeal and ulcer-protective effects of violacein isolated from *Chromobacterium violaceum* in Wistar rats
Fundam Clin Pharmacol, 2009

mais 3 referências

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9 Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): a natural product recently approved for cutaneous T-cell lymphoma
J Antibiot, 2011

Thus, the aim of this study was to evaluate the antitumor activity of crude extracts of *Chromobacterium* sp isolates from Minas Gerais and Amazonas, Brazil, and to establish a relationship between their differences in secondary metabolite compositions. The crude extracts showed cytotoxic activities with different potency and selectivity toward human tumor cell lines presented in this study. The presence or absence of compounds FK228 and violacein could not explain differences in antiproliferative activity demonstrated by extracts suggesting that other components are responsible for the antiproliferative activity.

Material and Methods

Bacterial strains

Four isolates used in this study are preserved in the Brazilian Collection of Industrial and Environmental Microorganisms (CBMAI, CPQBA, UNICAMP, Campinas, SP, Brazil). The isolates were recovered from water samples in Rio Preto da Eva (CBMAI 308 and 310) and Presidente Figueiredo (CBMAI 307) municipalities in Amazonas, Brazil, and one of them (CBMAI 592) was isolated from soil samples of Serra do Cipó National Park, in Minas Gerais, Brazil. *C. violaceum* -type strain (ATCC 12472^T, USA; CBMAI 534^T) was used as reference in experiments.

Phylogenetic analysis of the 16S rRNA genes

Genomic DNA of *Chromobacterium* sp isolates was used to amplify 16S rRNA gene with the bacterial primer set 27f and 1401r [10]. The sequencing was carried out using the set of primers 28f (5′-GAG TTT GAT CCT GGC TCA G-3′), 782r (5′-ACC AGG GTA TCT AAT CCT GT-3′), 765f (5′-ATT AGA TAC CCT GGT AG-3′) and 1100r (5′-AGG GTT GGG GTG GTT G-3′) according to manufacturer instructions (Invitrogen, Brazil). Partial 16S rRNA sequences obtained from isolates were assembled in a contig using the phred/Phrap/CONSED program. The sequences were aligned using the CLUSTAL X program and analyzed with the MEGA software v.4. Evolutionary distances were derived from sequence-pair dissimilarities calculated as implemented in MEGA, using Kimura's DNA substitution model. The phylogenetic reconstruction was done using the neighbor-joining algorithm with bootstrap values calculated from 1000 replicate runs [10].

10 Análise da diversidade genética por MLSA e avaliação da atividade antitumoral de linhagens de *Chromobacterium* sp[Master's thesis]: Instituto de Ciências Biomédicas, Universidade de São Paulo;
2009

Crude extract preparation

Extracts derived from the metabolism of *Chromobacterium* sp isolates were obtained after strain growth in nutrient broth (Oxoid) medium at 30°C for 48 h at 150 rpm. The bacterial suspension (40-60 g cells) was centrifuged at 14.000*g* for 10 min at 4°C to recover cells. Crude extracts of bacterial cells were obtained by sequential extraction with chloroform, ethyl acetate and ethanol solvents. The first crude extract obtained after 3 h of extraction with 150 mL chloroform was designated as chloroform crude extract (ClCE). The second crude extract obtained after 6 h of extraction of the residue of the ClCE extract with 150 mL ethyl acetate was denominated ethyl acetate crude extract (AcCE). The last one was obtained with ethanol (150 mL) after 10 h of extraction from the resulting residue of the AcCE extract and was denominated ethanol crude extract (EtCE). The crude extracts (ClCE, AcCE, and EtCE) were concentrated under vacuum at 40°C (Büchi Rotovapor R200 with Büchi heating steam bath B490, Switzerland), until complete evaporation. The extracts were dissolved in dimethylsulfoxide (DMSO) and assayed for *in vitro* antitumor activity against human tumor cells. In addition, AcCE 310 and EtCE 310 extracts were evaluated for *in vivo* antitumor activity against a murine cancer model - solid Ehrlich tumor.

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Table 1
Cytotoxic activity, reported as TGI values, of crude extracts of *Chromobacterium* sp isolates tested against human tumor cell lines.

Table 2
Cytotoxic activity, reported as TGI values, of crude extracts of *Chromobacterium* sp isolates tested against human tumor cell lines.

References

1. Newman DJ, Cragg GM. Microbial antitumor drugs: natural products of microbial origin as anticancer agents. Curr Opin Investig Drugs 2009; 10: 1280-1296. Link
2. Hungria M, Astolfi-Filho S, Chueire LM, Nicolas MF, Santos EB, Bulbol MR, et al. Genetic characterization of *Chromobacterium* isolates from black water environments in the Brazilian Amazon. Lett Appl Microbiol 2005; 41: 17-23, doi: 10.1111/j.1472-765X.2005.01724.x. Link

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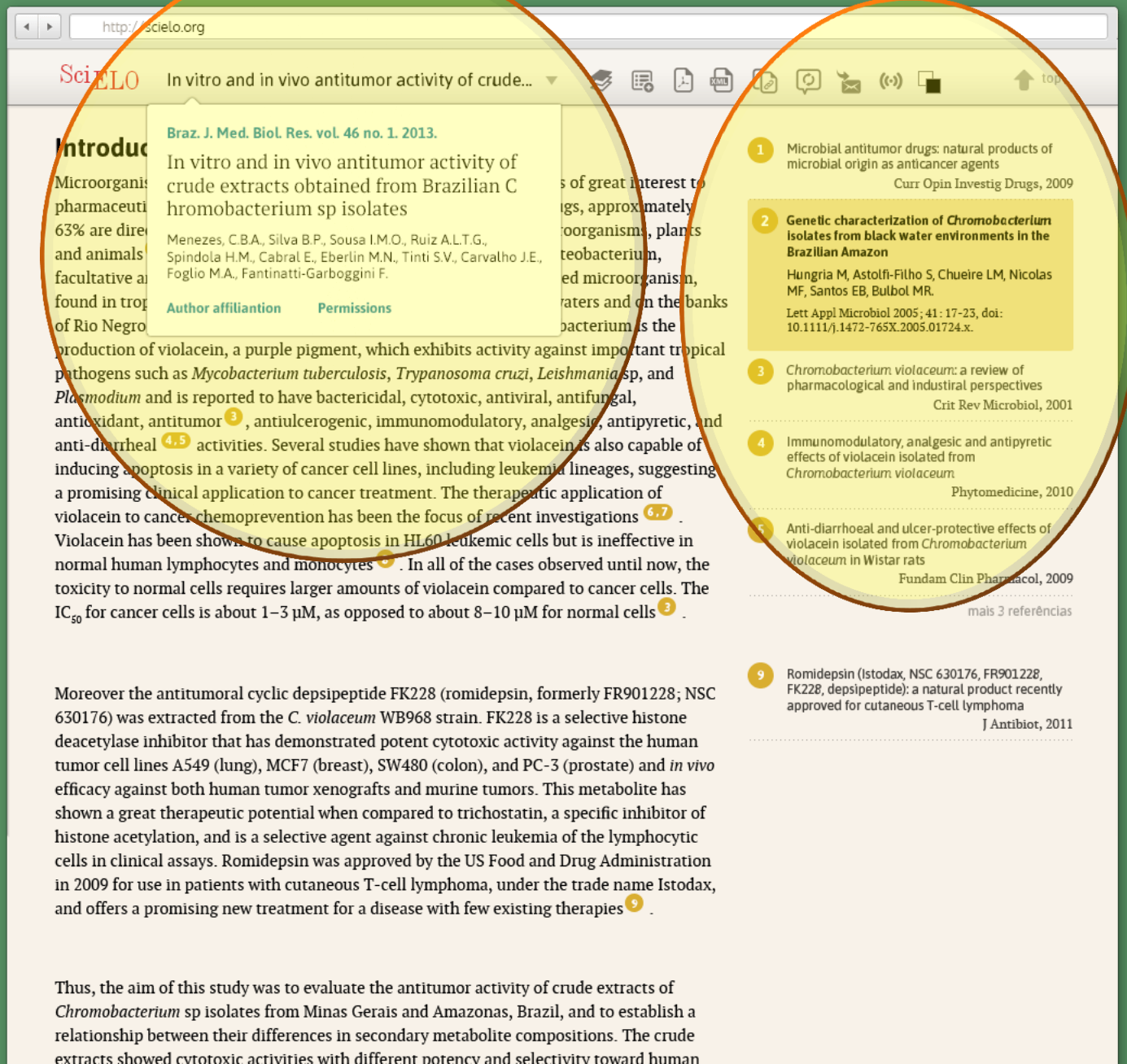

Introduc

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J Antibiot, 2011

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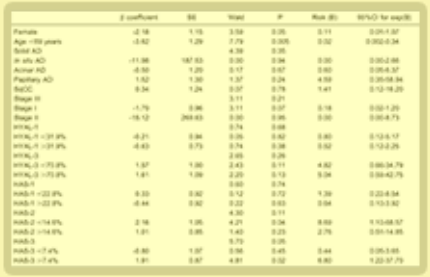

Table 1
Cytotoxic activity, reported as TGI values, of crude extracts of *Chromobacterium* sp isolates tested against human tumor cell lines.

Table 2
Cytotoxic activity, reported as TGI values, of crude extracts of *Chromobacterium* sp isolates tested against human tumor cell lines.

References

Crude extracts of bacterial cells were obtained by sequential extraction with chloroform, ethyl acetate and ethanol solvents. The first crude extract obtained after 3 h of extraction with 150 mL chloroform was designated as chloroform crude extract (ClCE). The second crude extract obtained after 6 h of extraction of the residue of the ClCE extract with 150 mL ethyl acetate was denominated ethyl acetate crude extract (AcCE). The last one was obtained with ethanol (150 mL) after 10 h of extraction from the resulting residue of the AcCE extract and was denominated ethanol crude extract (EtCE). The crude extracts (ClCE, AcCE, and EtCE) were concentrated under vacuum at 40°C (Büchi Rotovapor R200 with Büchi heating steam bath B490, Switzerland), until complete evaporation. The extracts were dissolved in dimethylsulfoxide (DMSO) and assayed for *in vitro* antitumor activity against human tumor cells. In addition, AcCE 310 and EtCE 310 extracts were evaluated for *in vivo* antitumor activity against a murine cancer model - solid Ehrlich tumor.

	β coefficient	SE	Wald	P	Risk (B)	95%CI for exp(B)
Female	-2.18	1.15	3.59	0.05	0.11	0.01-1.07
Age <69 years	-3.62	1.29	7.79	0.005	0.02	0.002-0.34
Solid AD			4.39	0.35		
in situ AD	-11.98	187.53	0.00	0.94	0.00	0.00-2.66
Acinar AD	-0.50	1.20	0.17	0.67	0.60	0.05-6.37
Papillary AD	1.52	1.30	1.37	0.24	4.59	0.35-58.94
SqCC	0.34	1.24	0.07	0.78	1.41	0.12-16.20
Stage III			3.11	0.21		
Stage I	-1.70	0.96	3.11	0.07	0.18	0.02-1.20
Stage II	-15.12	269.63	0.00	0.95	0.00	0.00-8.73
HYAL-1			0.74	0.68		
HYAL-1 <31.9%	-0.21	0.94	0.05	0.82	0.80	0.12-5.17
HYAL-1 >31.9%	-0.63	0.73	0.74	0.38	0.52	0.12-2.25
HYAL-3			2.65	0.26		
HYAL-3 <70.8%	1.57	1.00	2.43	0.11	4.82	0.66-34.79
HYAL-3 >70.8%	1.61	1.09	2.20	0.13	5.04	0.59-42.75
HAS-1			0.60	0.74		
HAS-1 <22.8%	0.33	0.92	0.12	0.72	1.39	0.22-8.54
HAS-1 >22.8%	-0.44	0.92	0.22	0.63	0.64	0.10-3.92
HAS-2			4.30	0.11		
HAS-2 <14.6%	2.16	1.05	4.21	0.04	8.69	1.10-68.57

References

Encaminhamentos

adoção da marcação do PMC – textos completos em XML

- periódicos ciências da saúde até dez 2013
- todos os periódicos até dez 2014
- domínio da tecnologia pelo SciELO
- domínio da tecnologia pelas empresas brasileiras
- contratação de empresas e serviços estrangeiros

estabilizar estrutura de custos e fontes de custeio

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Obrigado !