Current Topics in Pharmacology
Vol. 17, *1*, 2013

Mini-Review

Screening of Brazilian plants for anticancer activity: An overview

Marcilia P. Costa, Bruno C. Cavalcanti, Daniel P. Pinheiro, Assuero S. Meira, Levy S. Morais, Igor Bonfim, Manoel O. Moraes and Cláudia Pessoa*
National Laboratory of Experimental Oncology, Department of Physiology and Pharmacology, Federal University of Ceará, Fortaleza, Brazil

ABSTRACT

The Brazilian flora, the most diverse in the world, is considered an important source of natural richness. Natural products have long been an exceptional source of therapeutic agents, and still serve as an excellent source for new drug discovery. In the last decades, small organic molecules derived from plants have provided a number of useful anticancer drugs. In Brazil, screening programs have been established as a strategy to identify potentially bioactive substances. Currently, more constituents of plants are being investigated for their anticancer activities. This review shows that Brazil ranks 13th in publications on natural products related to oncology and compares the number of publications among Brazilian institutions. The Federal University of Ceará (UFC) is the 2nd Brazilian institution in the number of works in this area. Among the research groups in UFC, it is important to highlight the contributions of the Brazilian National Laboratory of Experimental Oncology (LabNOE) in searching for new potential anticancer molecules. This study also describes results of extensive anticancer studies of crude extracts and isolated compounds conducted by the laboratory (LabNOE) in the past years.

*Corresponding author: Cláudia Pessoa, Departamento de Fisiologia e Farmacologia, Universidade Federal do Ceará, R. Coronel Nunes de Melo, 1127, Caixa Postal 3157, 60430-270, Fortaleza-CE, Brazil. cpessoa@ufc.br

KEYWORDS: Brazilian flora, natural products, anticancer drugs, active compounds

INTRODUCTION

Mortality that results from the common forms of cancer is still unacceptably high. According to global cancer statistics released by the American Cancer Society, the total number of deaths from cancer in 2007 was 7.6 million, or about 20,000 deaths each day, with 38% in developed countries and 62% in developing countries. By 2050, 27 million new cancer cases and 17.5 million cancer deaths are projected to occur in the world [1]. The control of cancer, the second leading cause of death worldwide, may benefit from the potential of alternative therapies [2].

Current drugs used in cancer treatment are highly toxic and often non-specific to cancer cells, and thus, conventional chemotherapy is frequently associated with the development of drug resistance and systemic toxicity, thereby limiting drug efficacy [3]. Therefore, the low selectivity of most current anticancer agents makes the search for new molecules with more selective action and fewer side effects indispensable and challenging [4].

Natural products have long been an excellent source of pharmaceutical agents, and still serve as an excellent source for modern drug discovery and development, as indicated by the comparatively large number of chemical substances of natural origin currently under clinical trials [5, 6, 7].

For over 40 years, small organic molecules derived naturally from microbes and plants have provided a number of useful cancer chemotherapeutic drugs. The search for naturally occurring lead compounds of this type has continued in the recent years, with the constituents of marine fauna and flora as well as those of terrestrial microorganisms and plants being investigated for their anticancer activities [8]. In the field of natural products research, in addition to bioactivity- or mechanism of action-directed isolation approaches and characterization of active compounds, rational drug design-based modification and analog synthesis has helped to increase the number of promising natural product-derived antineoplastic agents currently in advanced clinical development or recently approved [9].

A total of five oncology drugs based on natural products were approved for marketing worldwide between the years 2007 and 2010, among which two are classified as natural products (Yondelis™ and Istodax®) and three as semi-synthetic natural products (Torisel™, Ixempra™ and Afinitor®) [10].

The discovery and introduction to the market of paclitaxel, the vinca alkaloids, etoposide, camptotheca alkaloids and many antibacterial drugs have demonstrated the importance of drug discovery programs based on natural products [11, 12]. According to Newman & Cragg [13], of a total of 155 anticancer agents approved for use in Western medicine and Japan since the 1940s, 47% were classified as natural products *per se* (14%), semi-synthetic derivatives of natural products (28%), or otherwise derived from natural products (5%). Also, in addition to being a proven and important source of drug leads, natural products-derived drugs also contribute significantly to the profitability of many pharmaceutical companies [14].

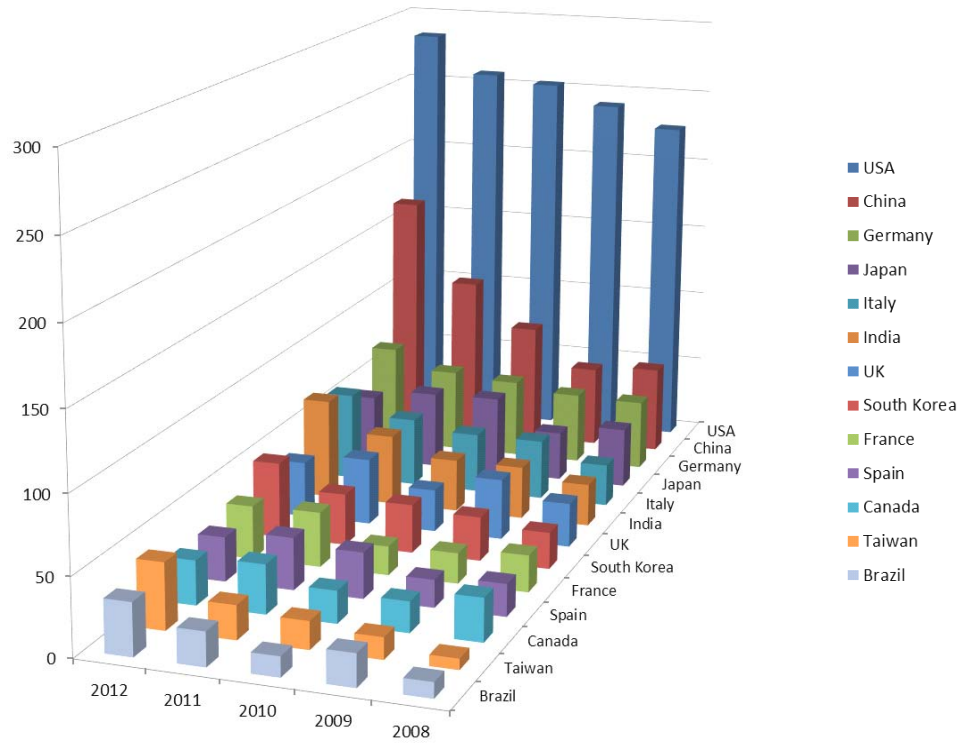
There is an impressive number of higher plant-derived anticancer drugs of diverse structural types both in present clinical use and in clinical trials as antineoplastic candidates, such as curcumin (extracted from *Curcuma longa* Linn; colon and pancreatic cancer), epigallocatechin gallate (extracted from green tea; breast and prostate cancer), and soy isoflavones (breast and prostate cancer) [5, 7, 12, 15]. This suggests that higher plants will continue to be an important and valuable resource for anticancer drug discovery, especially since 300,000-500,000 such species are known, and these represent about 15% of the taxonomically authenticated global organism biodiversity [16]. Moreover, probably less than 20% of the known plants on earth have ever been subjected to laboratory investigation for potential therapeutic effects, and a smaller percentage still for possible anticancer activity [17].

The worldwide biodiversity provides a limitless source for discovering novel anticancer drugs. In a global search using the keywords “natural product*” and “cancer*” in the Web of Science (WOS) Database, we observed an increasing number of publications on natural products related to oncology in the last 5 years (Figure 1). The data from the WOS Database was analyzed using the software Vantage Point Version 7.0. These results demonstrate that studies on natural products are not exceeded and that researchers worldwide are investing efforts in discovering new molecules from natural sources. The United States leads the ranks of publications in this area and the NCI is the most prominent institution. Brazil ranks 13th in such publications, emerging as the leader in Latin America in studies on natural products related to oncology (Figure 1).

Brazil has a prominent position in the world’s biodiversity. The large biodiversity within the territory of Brazil puts the country in a strategic position to develop the rational and sustained exploration of new metabolites of therapeutic value [14]. The Brazilian flora, the most diverse in the world, has become an interesting spot to prospect for new chemical leads or hits due to its species diversity and associated chemical richness. Screening programs have been established in Brazil as a strategy to identify potentially active substances. High-throughput screening techniques allow the analysis of large numbers of extracts in a relatively short period of time, and can be considered one of the most efficient ways of finding new leads from natural products [11].

The Brazilian National Laboratory of Experimental Oncology (LabNOE) at the Federal University of Ceará has been dedicated for a long time to the study of mechanisms of action and toxicity of

a)



b)

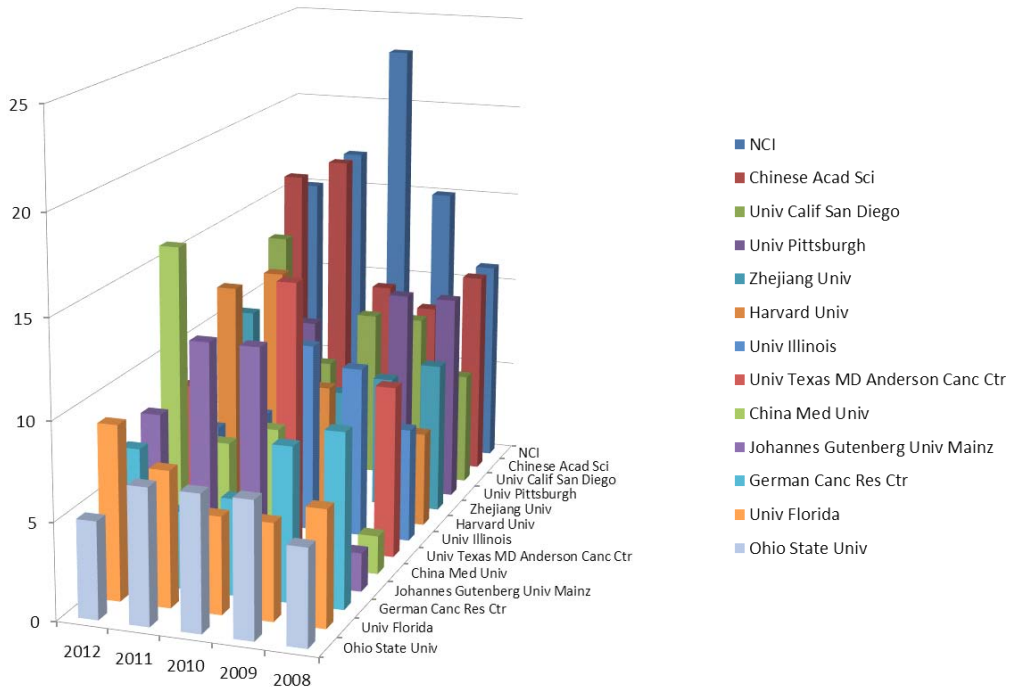


Figure 1. a) Countries vs number of publications related to natural products and cancer, in the last years. **b)** Wordwide institutions vs number of publications related to natural products and cancer, in the last years.

bioactive molecules from natural sources (plants, marine animals and microorganisms) as well as compounds obtained through chemical synthesis, aiming to discover new molecules with anticancer potential. Currently, our studies are supported by collaborations with more than 36 Brazilian universities and also with Brazilian and foreign research institutes. The Federal University of Ceará (UFC) is the 2nd Brazilian institution in the number of publications on natural products related to oncology, in the last 5 years. Among the research groups in UFC, it is important to highlight the contributions of our laboratory (LabNOE) in the search of new potential anticancer molecules (Figure 2).

Currently, around 30% of all compounds evaluated annually by LabNOE are derived from a variety of plant families. More than 2,000 plant compounds were analyzed in the last five years and some of them have shown very satisfactory results (Table 1 and 2) (Figure 3). The families Annonaceae, Fabaceae, Piperaceae and Simaroubaceae have revealed the greatest number of compounds with potent anticancer activity. Among the species more recently studied, *Calotropisprocera, Croton regelianus* and *Caprariabiflora* showed strong anticancer activity *in vitro* and *in vivo*.

Despite the great number of publications in the area of natural products and cancer, Brazil still lags far behind concerning the protection of the knowledge by patents. In this context, China and the USA emerge in the top positions (Figure 4). Most recently, the LabNOE group has protected some compounds; at least three patent applications are under development. The 2,3,9-trimethoxypterocarpan is one that had a patent deposit approved in the European office under the registration number of WO2013000054(A1). It is an isoflavonoid member originally isolated from *Platymiscium* floribundum and later synthesized by the group of Professor Martin Banwell in the Australian National University. Preliminary assays have shown an impressive cytotoxic effect in cancer cell lines and non-cytotoxic effect in peripheral blood mononuclear cells (PBMCs) [18]. Its effect was higher when tested against adherent cancer cell lines, exhibiting IC_{50} values around 2 µM (data not shown).

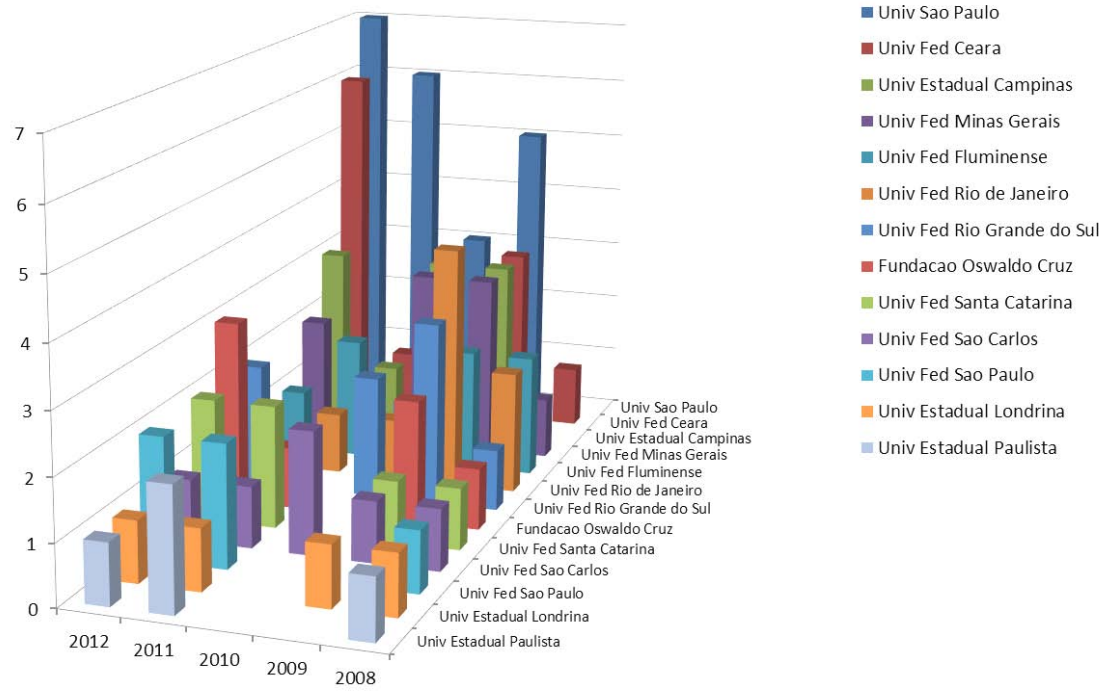


Figure 2. Brazilian Institutions vs number of publications related to natural products and cancer, in the last five years.

Table 1. Growth inhibitory effects of extracts or isolated compounds from Brazilian plants.

Family/Botanical name Localization; voucher no.	**Popular name**	**Plant part**	**Extracts or isolatedcompounds**	**Cell line (IC_{50})**	**References**
Celastraceae ***Maytenus ilicifolia*** **Paraná State; MBM253825**	Espinheira santa	Roots	Pristimerin	HL60 (0.61 µg/mL) K-562 (1.49 µg/mL) MDA/MB435 (0.26 µg/mL) SF-295 (0.57 µg/mL) HCT-8 (0.697 µg/mL)	[19]
Anacardiaceae ***Schinus terebinthifolius* var. raddianus** **Distrito Federal State; (UB)3753**	Aroeira	Leaves	Hexane extract	HL-60 (1.1 µg/mL)	[20]
			Dichloromethane extract	HL-60 (1.1 µg/mL)	
Annonaceae ***Annona crassiflora*** **Distrito Federal State; (UB)3700**	Aracutim	Roots	Ethanol extract of root bark	HL-60 (6.0 µg/mL)	[20]
			Ethanol extract of root wood	MDA-MB-435 (13.3 µg/mL)	
Annonaceae ***Duguetia furfuracea*** **Mato Grosso State; 023**	Araticum-miúdo	Stems	Duguetine	HCT-8/SF-295 (0.5 µg/mL)	[21]
			Duguetine β-N-oxide	SF-295 (0.6 µg/mL)	
			Alkaloid extract	SF-295 (0.6 µg/mL)	
Annonaceae ***Xylopia aromatica*** **Distrito Federal State; (UB)3699**	Pimenta de macaco	Roots	Hexane extract of root wood	HL-60 (5.9 µg/mL)	[20]
Annonaceae ***Xylopia sericeae*** **Pernambuco State; 48090**	Pindaíba	Roots	Kauren-19-oic acid	HL-60 (9.1 µg/mL)	[22]
			14-hydroxy-kaurane	HL-60 (>25 µg/mL)	
			Xylopic acid	HL-60 (>25 µg/mL)	
Clusiaceae ***Calophyllum brasiliense*** **Distrito Federal State; (UB)3754**	Guanandi	Roots	Dichloromethane extract of roots	MDA-MB-435 (3.0 µg/mL)	[20]

Table 1 continued..

Clusiaceae ***Kielmeyera coriacea*** **Distrito Federal State; (UB)3745**	Pau-santo	Roots/Stems	Hexane extract of stem bark	HCT-8 (16.3 µg/mL)	[20]
			Hexane extract of stem wood	HCT-8 (7.8 µg/mL)	
			Hexane extract of root wood	HCT-8 (5.4 µg/mL)	
			Hexane extract of root bark	HCT-8 (5.2 µg/mL)	
Euphobiaceae ***Croton regelianus*** **Ceará State; 24460**	Velame-de-cheiro	Leaves	Essential oil of leaves	HL-60 (22.2 µg/mL)	[23]
			Ascaridole	HL-60 (6.3 µg/mL)	
Euphobiaceae ***Croton argyrophylloides*** **Ceará State; 32444**	Marmeleiro prateado	Barks	Ent-kaurenediterpene 1	HCT-8 (5.2 µg/mL)	[24]
			Ent-kaurenediterpene 2	HCT-8 (1.5 µg/mL)	
Fabaceae ***Pterogyne nitens*** **São Paulo State; SP 204319b**	Bálsamo	Leaves	Nitensidine E	HL-60 (3.6 µg/mL)	[25]
Flacourtiaceae ***Casearia sylvestris* var. lingua** **Distrito Federal State; (UB)3693**	Erva-de-lagarto	Roots/Stems	Ethanol extract of root bark	MDA-MB-435 (18.0 µg/mL)	[20]
			Hexane extract of root wood	MDA-MB-435 (1.1 µg/mL)	
			Hexane extract of stem bark	HCT-8 (0.1 µg/mL)	
			Hexane extract of stem wood	MDA-MB-435 (0.5 µg/mL)	
		Leaves/Fruits	Hexane extract of leaves	HL-60 (1.4 µg/mL)	
			Hexane extract of fruits	MDA-MB-435 (18.2 µg/mL)	
Apocynaceae ***Himatanthus obovatus*** **Distrito Federal State; (UB)3678**	Tiborna	Leaves/Roots	Ethanol extract of leaves	SF-295 (21.8 µg/mL)	[20]
			Ethanol extract of root wood	MDA-MB-435 (10.9 µg/mL)	
Piperaceae ***Pothomorphe peltata*** **Amazonas State; 210168**	Caapeba	Roots	4-Nerolidylcatechol	HL-60 (6.17 µg/mL)	[26]

Table 1 continued..

Salicaceae ***Casearia oblique*** **São Paulo State; IAC46529**	Guaçatonga-vermelha	Leaves/Twigs	Caseobliquin A	HCT-8 (>5.0 µg/mL)	[27]
			rel-6β-Hydroxyzuelanin-2β-benzoate	HCT-8 (0.13 µg/mL)	
			rel-2α-Hydroxyzuelanin-6β-benzoate (Mix)		
			2β-Hydroxyzuelanin-6β-cinnamate	HCT-8 (>5.0 µg/mL)	
Sapindaceae ***Cupania vernalis* Cambess** **Distrito Federal State; (UB)3695**	Camboatã vermelho	Leaves	Hexane extract	MDA-MB-435 (4.0 µg/mL)	[20]
Sapindaceae ***Magonia pubescens*** **Distrito Federal State; (UB)3702**	Tingui	Roots	Ethanol extract of root wood	MDA-MB-435 (7.9 µg/mL)	[20]
Sapindaceae ***Serjania lethalis*** **Distrito Federal State; (UB)3716**	Timbó	Roots/Stems	Ethanol extract of stem bark	HCT-8 (8.0 µg/mL)	[20]
			Hexane extract of root bark	SF-295 (13.6 µg/mL)	
Sapotaceae ***Pouteria torta Radlk*.** **Distrito Federal State; (UB)3674**	Curiola	Roots	Ethanol extract of root wood	MDA-MB-435 (21.0 µg/mL)	[20]
Simaroubaceae ***Simarouba versicolor*** **Distrito Federal State; (UB)3724**	Pau-paraíba	Roots/Fruits	Hexane extract of root bark	HCT-8 (0.5 µg/mL)	[20]
			Ethanol extract of root bark	HCT-8/SF-295 (0.1 µg/mL)	
			Ethanol extract of fruits	HCT-8 (4.3 µg/mL)	
Simaroubaceae ***Picrolemma spruce*** **Amazonas State; Silva 5729&5730**	Caferana	Roots/Stems	Isobrucein B	HCT-8 (0.024 µg/mL)	[28]
			Neosergeolide	HCT-8 (0.005 µg/mL)	
			1,12-diacetylisobrucein B	HL-60 (11.77 µg/mL)	
			12-acetylneosergeolide	SF-295/HL-60 (0.51 µg/mL)	
Zingiberaceae ***Renealmia alpinia* (Rottb.)** **Distrito Federal State; (UB)3719**	Pacoseroca	Rhizome	Hexane extract	SF-295 (5.9 µg/mL)	[20]
			Dichloromethane extract	SF-295 (10.5 µg/mL)	

Table 1 continued..

Anacardiaceae ***Myracrodruon urundeuva* Fr. All.** **Ceará State; 34865**	Aroeira-do-sertão	Seeds	Ethanol extract	HL-60 (12.5 µg/mL) MDA-MB-435 (>50 µg/mL) SF-295 (25.1 µg/mL) HCT-8 (>50 µg/mL)	[29]
Asclepiadaceae ***Calotropis procera*** **Ceará State; 34706**	Algodão-de-seda	Stem	Ethyl acetate extract	HL-60 (1.6 µg/mL) B-16/F10 (2.0 µg/mL)	[30]
			Acetone extract	CEM (1.4 µg/mL) HCT-8 (0.8 µg/mL)	
Asteraceae ***Blainvillea rhomboidea*** **Ceará State; 33,879**	Erva-palha	Aerial parts	Luteolin	HCT-8 (3.37 µg/mL)	[31]
			7-O-metyl-luteolin	HCT-8 (2.71 µg/mL)	
Boraginaceae ***Cordia leucocephala*** **Rio Grande do Norte State; MOSS8827**	Molequeduro	Roots	(+)-Cordiaquinone J	HL-60 (2.7 µM) HCT-8 (4.9 µM) SF295 (6.6 µM) MDA-MB-435 (5.1 µM) PBMC (10.4 µM)	[32]
Calophyllaceae ***Kielmeyera coriacea* Mart. &Zucc.** **Distrito Federal State; 3745**	Pau-santo	Root	Mixture of δ-tocotrienol (1) and its dimer (2)	HL-60 (8.08 µg/mL) HCT-8 (13.02 µg/mL) SF-295 (23.58 µg/mL) MDA-MB-435 (16.39 µg/mL)	[33]
Fabaceae ***Copaifera langsdorffii*** **Minas Gerais State; 19597**	Copaíba	Leaves	Methanol extract	MCF-7 (12.9 µg/mL)	[34]
Salicaceae ***Casearia sylvestris* Swartz** **São Paulo State; AGS04, AGS05, AGS06, AGS13, AGS19**	Guaçatonga	Leaves	Caseargrewiin F	L-929 (1.09 µM) MOLT-4 (0.09 µM) MDA/MB-435 (0.13 µM) HCT-8 (0.15 µM) SF-295 (0.17 µM)	[35]
Verbenaceae ***Lantana fucata*** **Minas Gerais State; 16204**	Camará	Leaves	Methanol extract	MCF-7 (5.7 µg/mL)	[34]

Table 1 continued..

Casearia ***Casearia rupestris*** **São Paulo State; IAC41542**	Guaçatunga grande	Leaves	Casearupestrins A	HL-60 (0.10 µg/mL) MDA-MB-435 (0.36 µg/mL) HCT-8 (0.13 µg/mL) SF-295 (0.36 µg/mL)	[36]
			Casearupestrins B	HL-60 (0.85 µg/mL) MDA-MB-435 (1.3 µg/mL) HCT-8 (0.28 µg/mL) SF-295 (0.28 µg/mL)	
			Casearupestrins C	HL-60 (>5 µg/mL) MDA-MB-435 (>5µg/mL) HCT-8 (>5 µg/mL) SF-295 (>5 µg/mL)	
			Casearupestrins D	HL-60 (0.25 µg/mL) MDA-MB-435 (0.93 µg/mL) HCT-8 (0.25 µg/mL) SF-295 (0.43 µg/mL)	
Scrophulariaceae ***Capraria biflora*** **Ceará State; 30848**	Chá-do-rio	Roots	Biflorin	M14 (2.34 µg/mL) UACC-257 (1.48 µg/mL) UACC-62 (1.67 µg/mL) MDA-MB-435 (0.65 µg/mL) B16 (10.12 µg/mL) HL-60 (1.95 µg/mL) CEM (1.02 µg/mL) K562 (2.43 µg/mL) MCF-7 (0.43 µg/mL) MDA-MB-231 (14.61 µg/mL) MX-1 (1.11 µg/mL) NCI H266 (0.86 µg/mL) NCI H23 (0.58 µg/mL) PC-3 (6.09 µg/mL) SF-295 (0.63 µg/mL) HCT-8 (0.88 µg/mL)	[37]

Table 1 continued..

Annonaceae ***Guatteriopsis friesiana*** **Amazonas State; 7341**	Envireira	Leaves	Essential oil from the leaves	HL-60 (9.4 µg/mL) MDA-MB-435 (9.4 µg/mL) HCT-8 (1.7 µg/mL) SF-295 (6.7 µg/mL)	[38]
			α-Eudesmol	HL-60 (5.1 µg/mL) MDA-MB-435 (19.4 µg/mL) HCT-8 (10.2 µg/mL) SF-295 (9.7 µg/mL)	
			β-Eudesmol	HL-60 (25.1 µg/mL) MDA-MB-435 (>25 µg/mL) HCT-8 (24.9 µg/mL) SF-295 (24.1 µg/mL)	
			γ-Eudesmol	HL-60 (10.2 µg/mL) MDA-MB-435 (20.6 µg/mL) HCT-8 (8.3 µg/mL) SF-295 (7.1 µg/mL)	

Table 2. Anticancer activity of extracts or isolated compounds from Brazilian plants in experimental tumor.

Family/Botanical name Localization; voucher no.	**Popular name**	**Extracts or isolated compounds**	**Dose ($mg.kg^{-1}$ day^{-1})**	**Tumor**	**Inhibition (%)**	**References**
Piperaceae ***Piper divaricatum*** **Ceará State; 38219**	Pimenta	Piperlonguminine	25 and 50 (i.p.)	Sarcoma 180	38.71 and 40.68	[39]
Asclepiadaceae ***Calotropis procera*** **Ceará State; 34706**	Algodão-de-seda	Latex of aerial parts	5 (i.p.) and 20 (p.o.)	Sarcoma 180	51.83	[40]
Asclepiadaceae ***Calotropis procera*** **Ceará State; 34706**	Algodão-de-seda	Extracts of Stem	250 (i.p.)	Sarcoma 180	64.3	[30]
Apocynaceae ***Himatanthus drasticus* (Mart.) Plumel** **Ceará State; 40408**	Janaguba, pau de leite, jasmin-manga	Soluble latex protein (HdLP)	10 and 20 (i.p.)	Sarcoma 180	36.46 and 34.22	[41]
				Walker 256 Carcinosarcoma	57.91 and 55.23	
Scrophulariaceae ***Capraria biflora*** **Ceará State; 30848**	Chá-do-rio	Biflorin	25 (i.p.)	B16 tumor	64.89	[37]
Annonaceae ***Guatteriopsis friesiana*** **Amazonas State; 7341**	Envireira	Leaves	50 and 100 (i.p.)	Sarcoma 180	43.4 and 54.2	[38]
Lamiaceae ***Hyptis pectinata*** **Alagoas State; MUFAL4071**	Sambacaitá	Whole plant	100 (i.p.)	Sarcoma 180	70.5	[42]

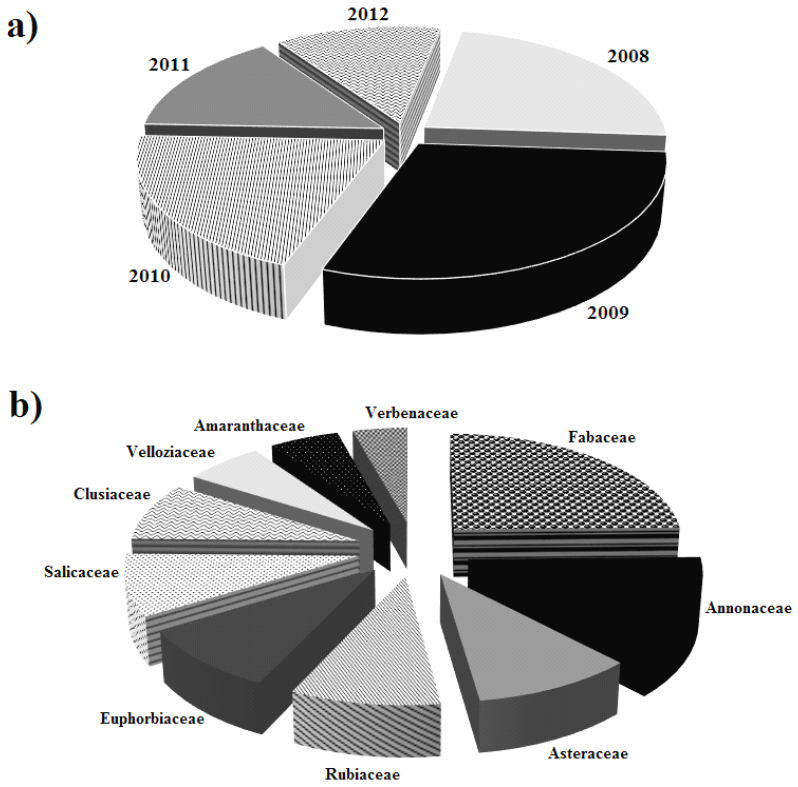


Figure 3. Analyses carried out on plant products by LabNOE. a) Number of crude extracts and isolated compounds analyzed in the last five years. b) Main plant families researched in the last years.

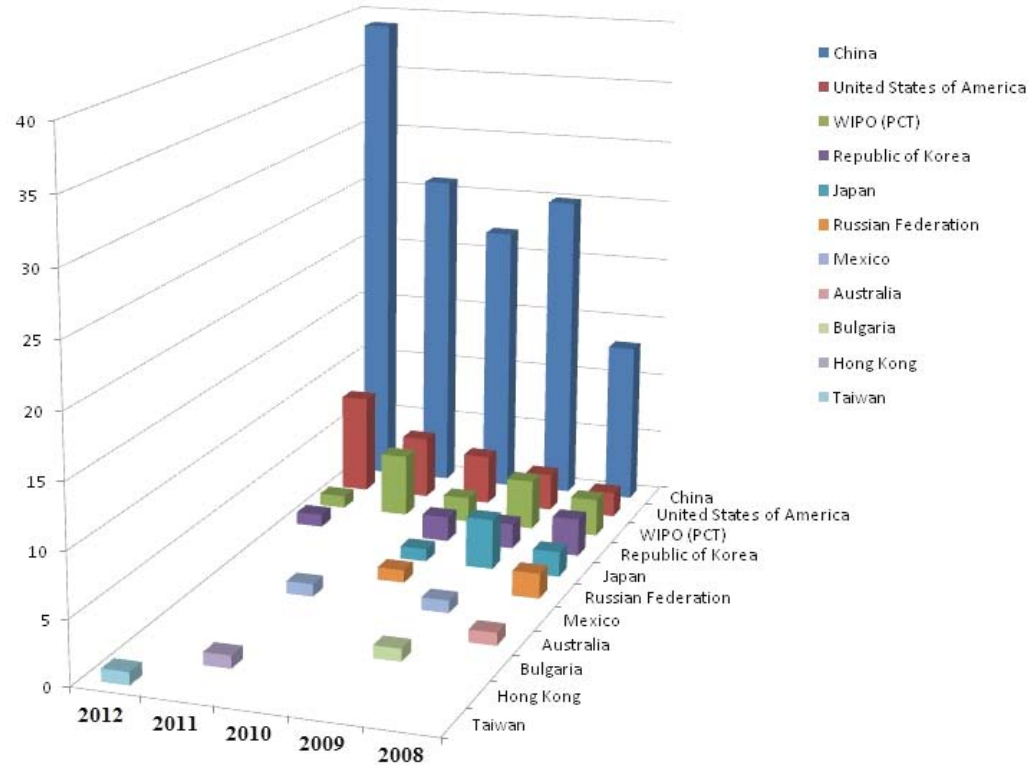


Figure 4. Countries vs number of patents related to natural products and cancer, in the last years.

Regarding plant studies, our screening program began over 10 years ago with the invaluable assistance of Prof. Dr. Gordon Cragg from the National Cancer Institute (NCI) of the USA, who kindly donated several tumor cell lines to our laboratory, allowing the evaluation of the cytotoxic potential of more than 10,000 Brazilian medicinal plant extracts and synthetic compounds. Several compounds with potent cytotoxicity have been isolated from plant extracts through studies in our laboratory (LabNOE). This study presents a review of the screening efforts of our laboratory during the period of 2008-2012 (Tables 1 and 2).

CONCLUSIONS AND OUTLOOK

In recent years, the scientific community has joined forces to investigate the Brazilian biodiversity. As a result of that, an increasing number of partnerships have been set up to search for pharmacological activities in phyto-derived compounds. Several of these have been studied and some have shown promising results as anticancer drugs in *in vitro* and *in vivo* assays. These outcomes have been a stimulus to increase the research of this huge resource so poorly explored.

Knowledge of new advances in cell biology will help us to better understand the plant-derived compounds, giving us the opportunity to discover new molecular mechanisms, resulting in more specific and less toxic bioactive molecules.

ACKNOWLEDGMENTS

We are indebted to Prof. Dr. Gordon M. Cragg for all the support he has given to our research group. The support received from CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico, Brazil) and FUNCAP (Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico, Brazil) to carry out this work is also gratefully acknowledged.

CONFLICT OF INTEREST STATEMENT

Conflict of interest doesn't exist for the authors.

REFERENCES

1. Garcia, M., Jemal, A., Ward, E. M., Center, M. M., Hao, Y., Siegel, R. L. and Thun, M. J. 2007, Global Cancer Facts & Figures, Atlanta, American Cancer Society.
2. Reddy, L., Odhav, B. and Bhoola, K. D. 2003, Pharm. Therap., 99, 1-13.
3. Leszczyniecka, M., Roberts, T., Dent, P., Grant, S. and Fisher, P. B. 2001, Pharm. Therap., 90, 105-156.
4. Cavalcanti, B. C., Barros, F. W. A., Cabral, I. O., Ferreira, J. R. O., Magalhães, H. I. F., Júnior, H. V. N., Silva, Jr. E. N., Abreu, F. C., Costa, C. O., Goulart, M. O. F., Moraes, M. O. and Pessoa, C. 2011, Chem. Res. Toxicol., 24, 1560-1574.
5. Butler, M. S. 2008, Nat. Prod. Rep., 25, 475-516.
6. Harvey, A. L. 2008, Drug Disc. Today, 13, 894-901.
7. Saklani, A. and Kutty, S. K. 2008, Drug Disc. Today, 13, 161-171.
8. Kinghorn, A. D., Chin, Y. W. and Swanson, S. M. 2009, Curr. Op. Drug Disc. Devel., 12, 189-196.
9. Lee, K. H. 2010, J. Nat. Prod., 73, 500-516.
10. Mishra, B. B. and Tiwari, V. K. 2011, Eur. J. Med. Chem., 46, 4769-4807.
11. Younes, R. N., Varella, A. D. and Suffredii, I. B. 2007, Clinics, 62, 763-768.
12. Shu, L., Cheung, K. L., Khor, T. O., Chen, C. and Kong, A. N. 2010, Cancer Met. Ver., 29, 483-502.
13. Newman, D. J. and Cragg, G. M. 2007, J. Nat. Prod., 70, 461-467.
14. Basso, L. A., da Silva, L. H. P., Fett-Neto, A. G., Azevedo, Jr. W. F., Moreira, I. S., Palma, M. S., Calixto, J. B., Filho, S. A., Santos, R. R., Soares, M. B. P. and Santos, D. S. 2005, Mem. Inst. Oswaldo Cruz, 100, 475-506.
15. Cragg, G. M., Kingston, D. G. I. and Newman, D. J. 2005, Boca Raton, CRC/Taylor & Francis.
16. Tan, G. T., Gylenhaal, C. and Soejarto, D. D. 2006, Curr. Drug. Targ., 7, 265-277.
17. Cragg, G. M., Grothaus, P. G. and Newman, D. J. 2009, Chem. Rev., 109, 3012-3043.
18. Militão, G. C. G., Bezerra, D. P., Pessoa, C., Moraes, M. O., Ponte, F. A. F., Lima, M. A. S., Silveira, E. R. and Costa-Lotufo, L. V. 2007, J. Nat. Med., 61, 196-199.
19. Costa, P. M., Ferreira, P. M., Bolzani, V. S., Furlan, M., de Freitas, F. M., Dos Santos, V. A., Corsino, J., Moraes, M. O., Costa-Lotufo, L. V., Montenegro, R. C. and Pessoa, C. 2008, Toxicol. in Vitro, 22(4), 854-863.

20. Mesquita, M. L., Paula, J. E., Pessoa, C., Costa-Lotufo, L. V., Moraes, M. O., Grougnet, R., Michel, S., Tillequin, F. and Espindola, L. S. 2009, J. Ethnopharm., 123, 439-445.
21. Silva, D. B., Tulli, E. C. O., Militão, G. C. G., Costa-Lotufo, L. V., Pessoa, C., Moraes, M. O., Albuquerque, S. and Siqueira, J. M. 2009, Phytomedicine, 16, 1059-1063.
22. Cavalcanti, B. C., Bezerra, D. P., Magalhães, H. I. F., Moraes, M. O., Lima, M. A. S., Silveira, E. R., Câmara, C. A. G., Rao, V. S., Pessoa, C. and Costa-Lotufo, L. V. 2009, J. App. Toxicol., 29, 560-568.
23. Bezerra, D. P., Marinho Filho, J. D. B., Alves, A. P. N. N., Pessoa, C., Moraes, M. O., Pessoa, O. D. L., Torres, M. C. M., Silveira, E. R., Viana, F. A. and Costa-Lotufo, L. V. 2009, Chem. Biodiv., 6, 1224-1231.
24. Santos, H. S., Barros, F. W. A., Albuquerque, M. R. J. R., Bandeira, P. N., Pessoa, C., Braz-Filho, R., Monte, F. J. Q., Leal-Cardoso, J. H. and Lemos, T. L. G. 2009, J. Nat. Prod., 72, 1884-1887.
25. Regasini, L. O., Castro-Gamboa, I., Silva, D. H. S., Furlan, M., Barreiro, E. J., Ferreira, P. M. P., Pessoa, C., Costa-Lotufo, L. V., Moraes, M. O., Young, M. C. M. and Bolzani, V. S. 2009, J. Nat. Prod., 72, 473-476.
26. Pinto, A. C. S., Silva, L. F. R., Cavalcanti, B. C., Melo, M. R. S., Chaves, F. C. M., Costa-Lotufo, L. V., Moraes, M. O., Andrade-Neto, V. F., Tadei, W. P., Pessoa, C., Vieira, P. P. R. and Pohlit, A. M. 2009, Eur. J. Med. Chem., 44, 2731-2735.
27. Vieira-Júnior, G. M., Gonçalves, T. O., Regasini, L. O., Ferreira, P. M. P., Pessoa, C., Costa-Lotufo, L. V., Torres, R. B., Boralle, N., Bolzani, V. S. and Cavalheiro, A. J. 2009, J. Nat. Prod., 72, 1847-1850.
28. Silva, E. C. C., Cavalcanti, B. C., Amorim, R. C. N., Lucena, J. F., Quadros, D. S., Tadei, W. P., Montenegro, R. C., Costa-Lotufo, L. V., Pessoa, C., Moraes, M. O., Nunomura, R. C. S., Nunomura, S. M., Melo, M. R. S., Andrade-Neto, V. F., Silva, L. F. R., Vieira, P. P. R. and Pohlit, A. M. 2009, Mem. Inst. Oswaldo Cruz, 104, 48-55.
29. Ferreira, P. M., Farias, D. F., Viana, M. P., Souza, T. M., Vasconcelos, I. M., Soares, B. M., Pessoa, C., Costa-Lotufo, L. V., Moraes, M. O., Carvalho, A. F. 2011, An. Acad. Bras. Cienc., 83(3), 1045-1058.
30. Magalhães, H. I. F., Ferreira, P. M. P., Moura, E. S., Torres, M. R., Alves, A. P. N. N., Pessoa, O. D. L., Costa-Lotufo, L. V., Moraes, M. O. and Pessoa, C. 2010, An. Acad. Bras. Cienc., 82, 407-416.
31. Gomes, R. F., Santos, H. S., Albuquerque, M. R. J. R., Pessoa, O. D. L., Costa Lotufo, L. V., Pessoa, C. O., Moraes, M. O. and Rodrigues, F. A. R. 2010, Quím. Nova, 33(5), 1122-1125.
32. Marinho-Filho, J. D. B., Bezerra, D. P., Araújo, A. J., Montenegro, R. C., Pessoa, C., Diniz, J. C., Viana, F. A., Pessoa, O. D. L., Silveira, E. R., Moraes, M. O. and Costa-Lotufo, L. V. 2010, Chem-Biol. Inter., 183, 369-379.
33. Mesquita, M. L., Araújo, R. M., Bezerra, D. P., Filho, R. B., de Paula, J. E., Silveira, E. R., Pessoa, C., Moraes, M. O., Costa-Lotufo, L. V. and Espindola, L. S. 2011, Bio. Med. Chem., 19(1), 623-630.
34. Santos, A. G., Ferreira, P. M. P., Vieira, Jr. G. M., Perez, C. C., Tininis, A. G., Silva, G. H., Bolzani, V. S., Costa-Lotufo, L. V., Pessoa, C. O. and Cavalheiro, A. J. 2010, Chem. Biodiv., 7, 205-215.
35. Santos, Jr. H. M., Oliveira, D. F., Carvalho, D. A., Pinto, J. M. A., Campos, V. A. C., Mourão, A. R. B., Pessoa, C., Moraes, M. O. and Costa-Lotufo, L. V. 2010, J. Nat. Med., 64, 231-238.
36. Vieira-Júnior, G. M., Dutra, L. A., Ferreira, P. M., Moraes, M. O., Costa-Lotufo, L. V., Pessoa, C. O., Torres, R. B., Boralle, N., Bolzani, V. S. and Cavalheiro, A. J. 2011, J. Nat. Prod., 74(4), 776-781.
37. Vasconcellos, M. C., Bezerra, D. P., Fonseca, A. M., Araújo, A. J., Pessoa, C., Lemos, T. L., Costa-Lotufo, L. V., Moraes, M. O. and Montenegro, R. C. 2011, Melan. Res., 21(2), 106-114.
38. Brito, A. C. S., Oliveira, A. C. A., Henriques, R. M., Cardoso, G. M. B., Bomfim, D. S., Carvalho, A. A., Moraes, M. O., Pessoa, C., Pinheiro, M. L. B., Costa, E. V. and Bezerra, D. P. 2012, Planta Med., 78,1-6.

39. Bezerra, D. P., Pessoa, C., Moraes, M. O., Alencar, N. M., Mesquita, R. O., Lima, M. W., Alves, A. P., Pessoa, O. D., Chaves, J. H., Silveira, E. R. and Costa-Lotufo, L. V. 2008, J. Appl. Toxicol., 28(5), 599-607.
40. Oliveira, J. S., Costa-Lotufo, L. V., Bezerra, D. P., Alencar, N. M. N., Marinho-Filho, J. D. B., Figueiredo, I. S. T., Moraes, M. O., Pessoa, C., Alves, A. P. N. N. and Ramos, M. V. 2010, Nau. Schm. Arch. Pharm., 382(2), 139-149.
41. Mousinho, K. C., Oliveira, C. C., Ferreira, J. R., Carvalho, A. A., Magalhães, H. I., Bezerra, D. P., Alves, A. P., Costa-Lotufo, L. V., Pessoa, C., de Matos, M. P., Ramos, M. V. and Moraes, M. O. 2011, J. Ethnopharm., 137(1), 421-426.
42. Barbosa, C. V., Aquino, P. G. V., Ribeiro-Júnior, K. A. L., Moura, F. B. P., Alexandre-Moreira, M. S., Sant'Ana, A. E. G., Ferreira, J. R. O., Moraes, M. O., Pessoa, C., Aguiar, J. S., Silva, T. G. and Araújo-Júnior, J. X. 2012, Pharm. Online, 3, 70-74.