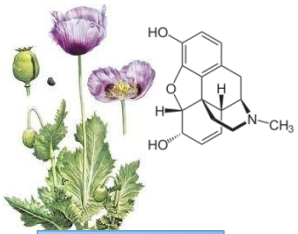
Natural Products Database from Brazilian Biodiversity, a Powerful Tool for Science, Technology and Innovation

Prof. Vanderlan S. Bolzani

Marilia Valli
Post-doctoral Researcher

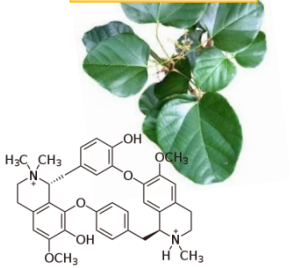
Timeline of a few Natural Products for Human Health



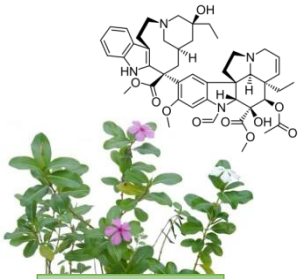
1804 — Morphine extracted from opium poppy

1899 — Acetylsalicylic acid commercialization

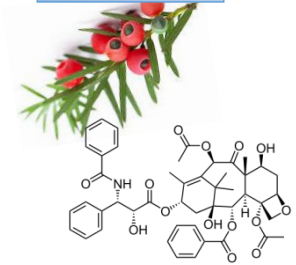
1928 — Discovery of penicillin



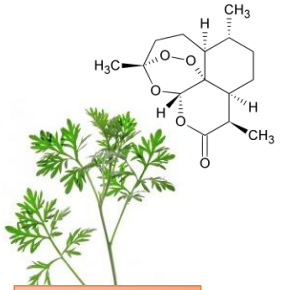
1942 — Use of tubocurarine as anaesthetic



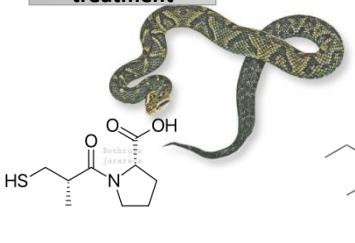
1963 — Vinca alkaloids, cancer treatment



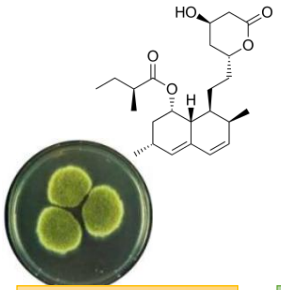
1971 — Taxol discovery



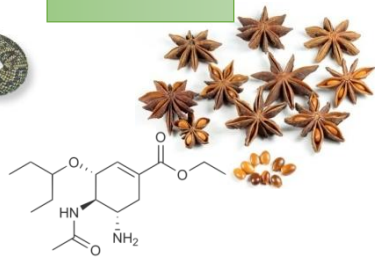
1972 — Artemisinin discovery



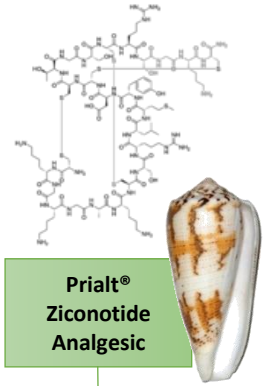
1981 — Captopril approval for hypertension treatment



1987 — Lovastatin approved as lipid-lowering agent



2000… — oseltamivir Tamiflu®

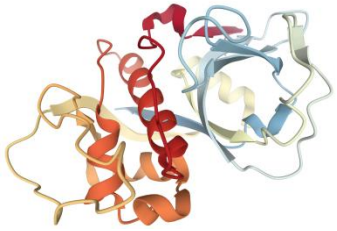


Prialt® Ziconotide Analgesic

Valli; Bolzani, AABC, 91(3), e20190208, 2019

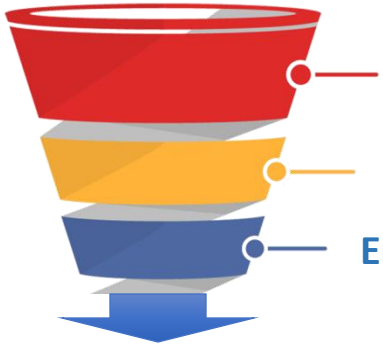
Natural Products Chemistry

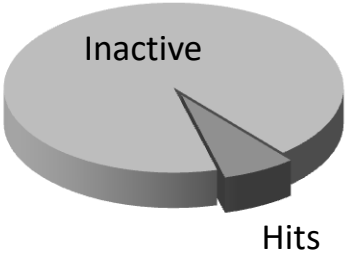
Database of Natural Products from Brazil



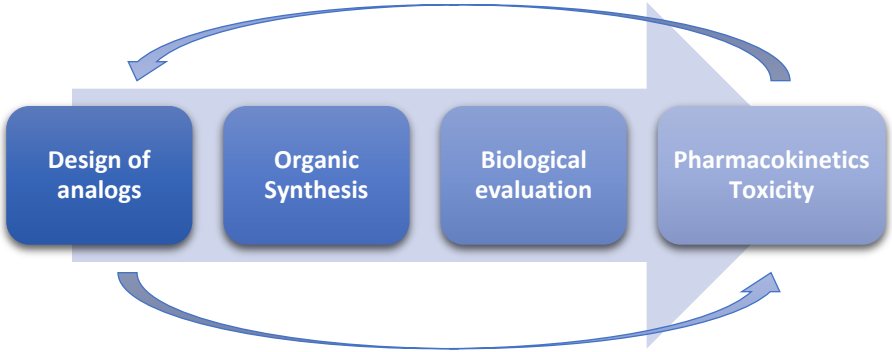
Molecular Target

Medicinal Chemistry

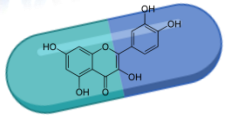




Lead optimization process



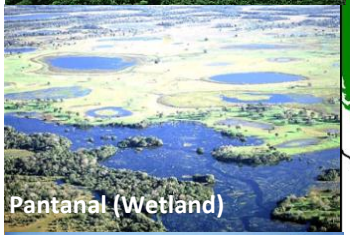
DRUG CANDIDATE

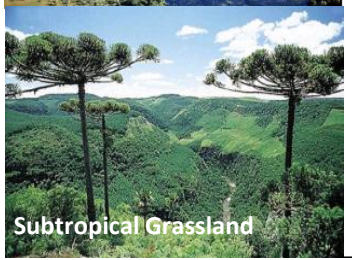


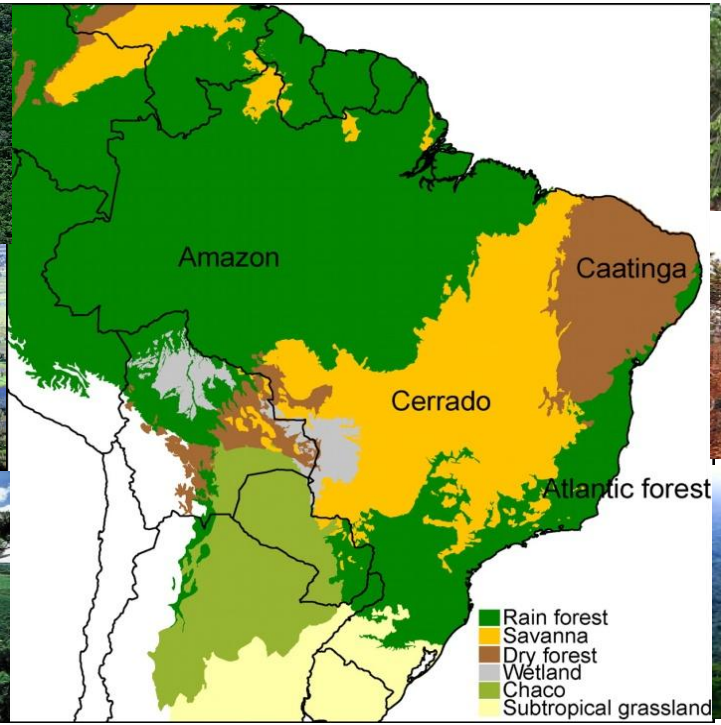
Brazil is a conservation priority and especially responsible for a change in concepts for sustainability

Brazil is included among the 17 megadiverse countries in the World has **9.5% of all known living species and 18% of all plant species**

Ecological relationships
Tropical environments







Valli; Bolzani, AABC, 91(3), e20190208, 2019

Historical background

♦1998 – Creation of Biota Program
"Conservation and Sustainable Use of the Diversity from Cerrado and Atlantic forest: Chemical Diversity and Prospecting for Potential Drugs"

1700 extracts from 1100 plants
150 extracts from endophytic fungi
Field trips: 25 (11 Cerrado e 14 Atlantic Forest)

CIBFar

INCT BioNat BIODIVERSIDADE E PRODUTOS NATURAIS

Joly et al. *Science, 328, 1358-1359, 2010*
Bolzani; Valli; Pivatto; Viegas, Jr., Pure Appl. Chem, 84(9), 1837-1846, 2012
Valli; Russo; Bolzani, *AABC, 90(1) 763-778, 2018*

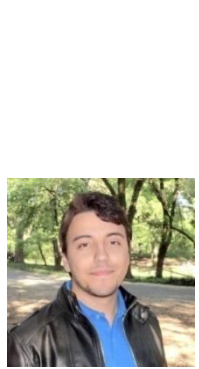
NuBBE Database

The 1st Natural Products Database from Brazilian Biodiversity

Extract chemical information from published data

Compile and generate info and descriptors

Make available




LQMC Laboratório de Química Medicinal e Computacional

NuBBE

Useful tool for:

- drug design/ molecular modeling
- dereplication and metabolomics
- chemotaxonomy

2010-2014

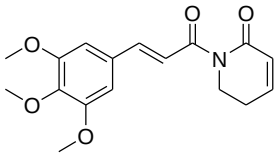
Version 1.0
640 compounds

Valli et al. J. Nat. Prod. 76(3), 439–444, 2013

NuBBE Database

32,000 papers
CNPq Platform

Inclusion Criteria
- Digital Object Identifier
- location



Compound

Metabolic Class

Reference

Common Name

SMILES

Dewick Biosynthesis

doi

IUPAC Name

InChI code

mol files

Molecular properties

NMR spectra

Natural Resource Origin

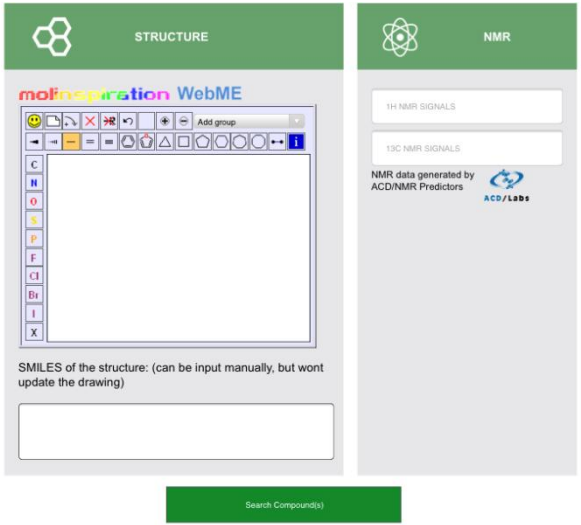
Biological Activity

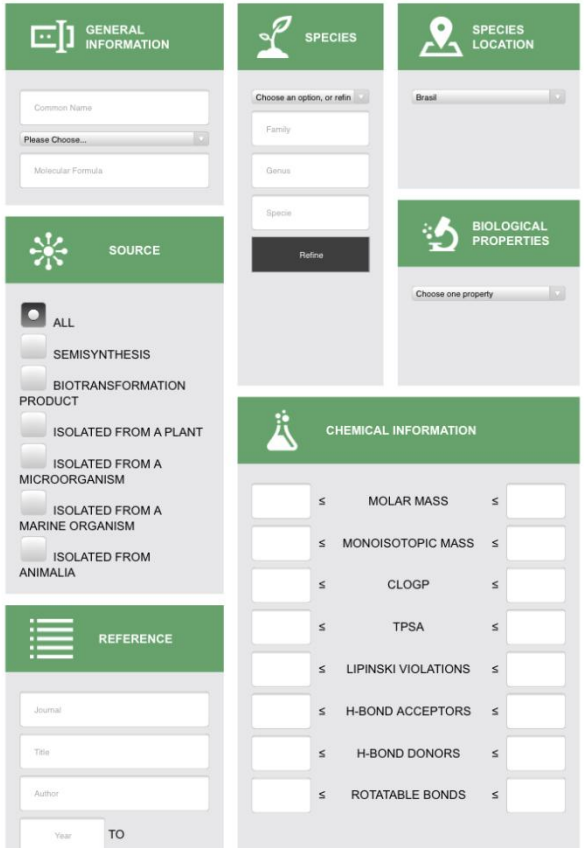
Taxonomy

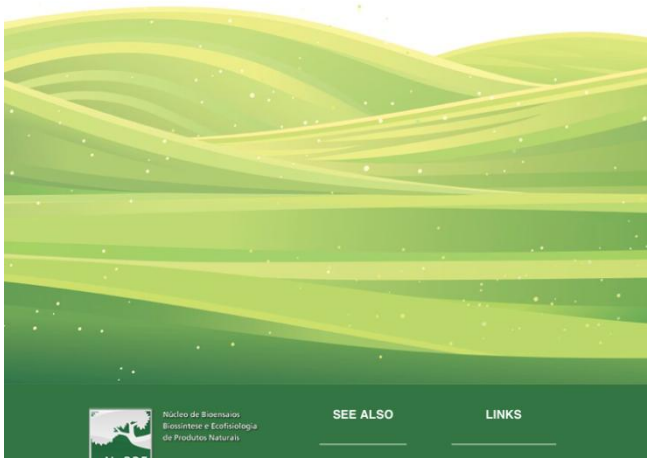
Geographic Location

Manually Introduced Data

Automatically generated Data







NuBBE Database Website

nubbe.iq.unesp.br/nubbeDB.html

Search compounds by:

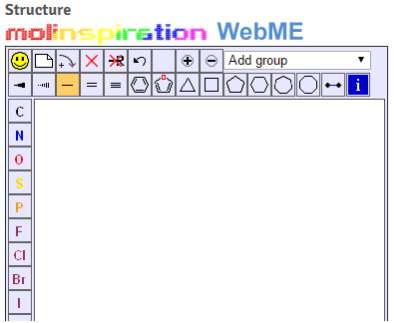
- Chemical structure
- Biological property
- Source
- Geographical location
- Molecular descriptors
- NMR signals

Molecular Properties

molinspiration cheminformatics

- **Molecular Mass**
- **Molecular Volume**
- ***cLogP* (Lipophilicity)**
- **TPSA (Topological Polar Surface Area)**
- **Hydrogen Bond Donors and Acceptors**
- **nRotb (Number of Rotatable Bonds)**
- **Violations of Lipinski's Rule of Five**

Search by structure using WebME tool, also from Molinspiration

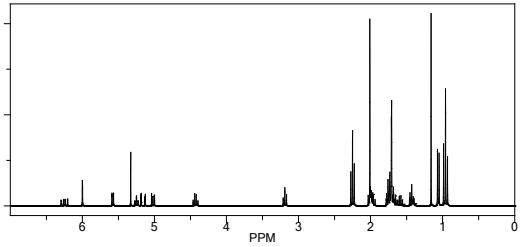


http://www.molinspiration.com/
Irwin, J. J., Shoichet, B. K. *J. Chem. Inf. Model., 45,* 177-182, 2005.

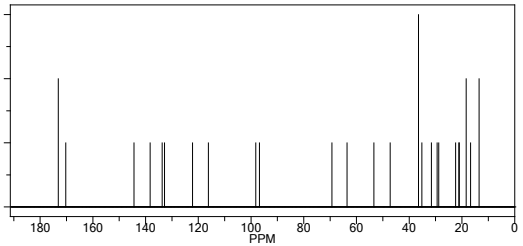
NMR prediction

^{1}H e ^{13}C NMR spectra are automatically predicted by *H and C NMR predictors command line* from *Advanced Chemistry Development, Inc.* (ACD/Labs, Canada).

The NMR Predictor uses HOSE code and neural net algorithms to provide accurate chemical shifts.

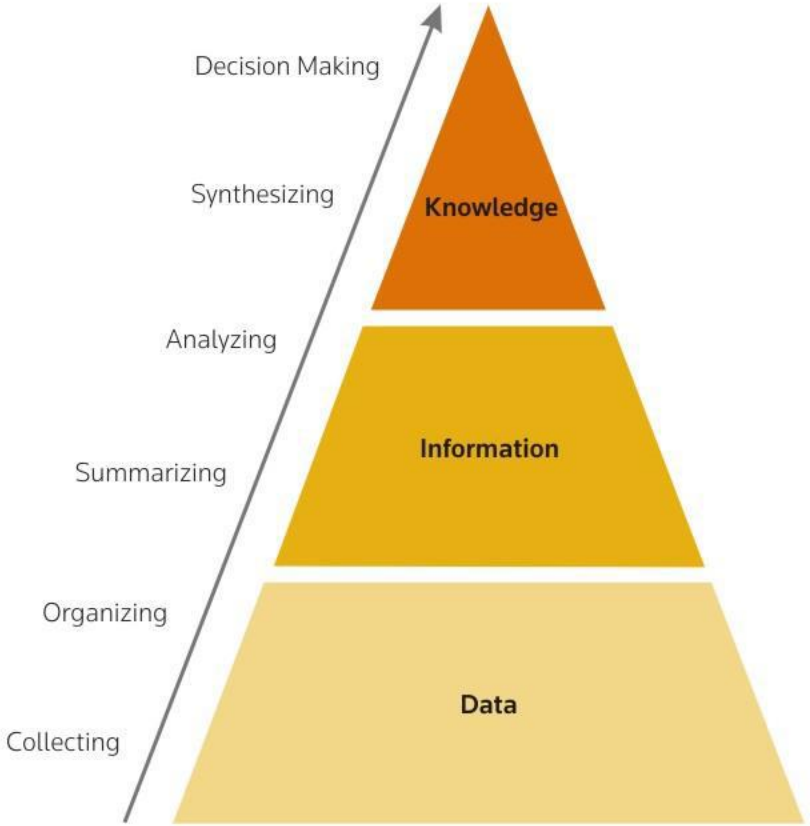


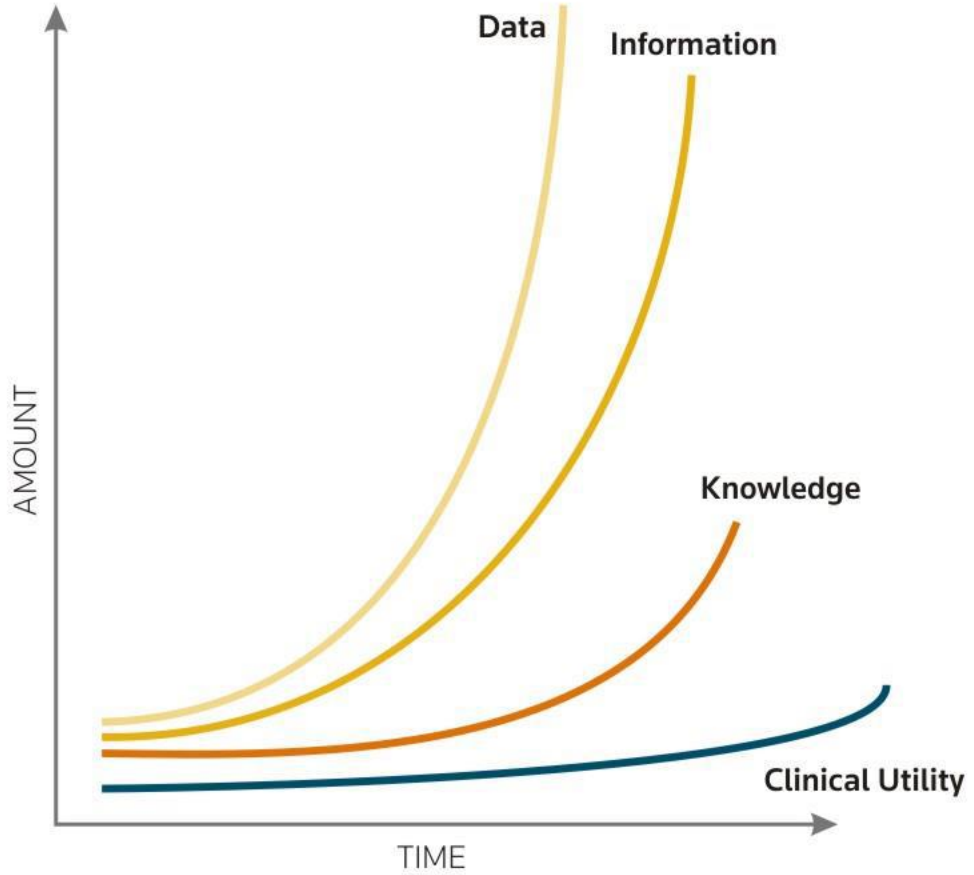
Parameters used for predictions:
^{1}H-NMR (600 MHz, spectral width 0-14 ppm)
^{13}C-NMR (150 MHz , spectral width 0-220 ppm)
65 thousand points
solvent is undefined (average of all common deuterated solvents).



https://www.acdlabs.com/company/media/pr/170814_nubbe.php

Data – Information – Knowledge



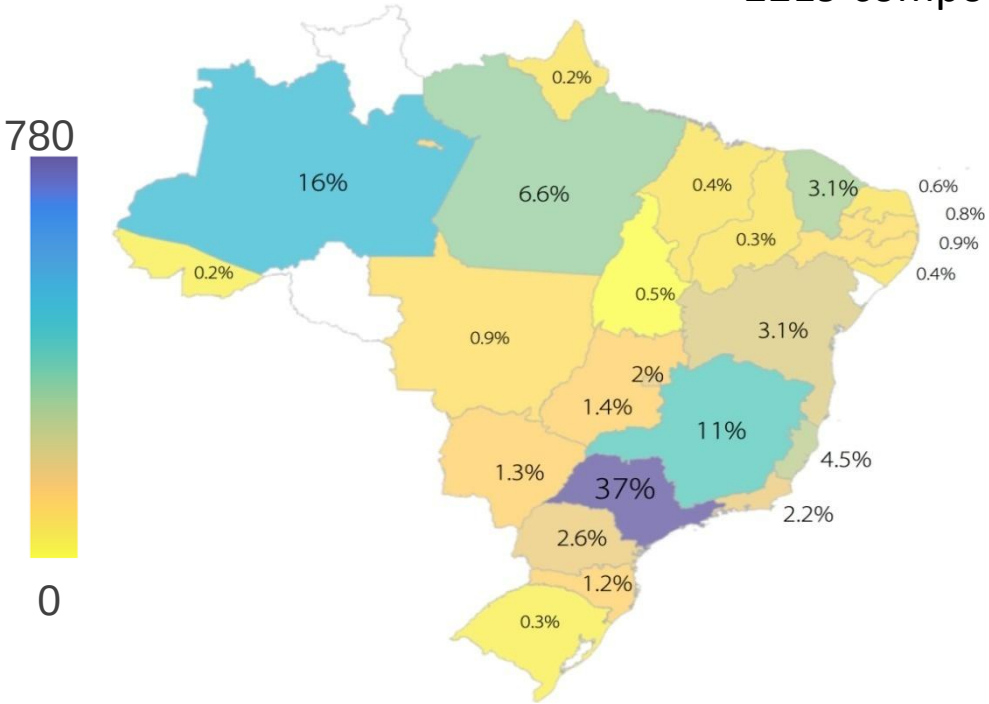


Delarcina, Integrity, Clarivate Analytics, 2019

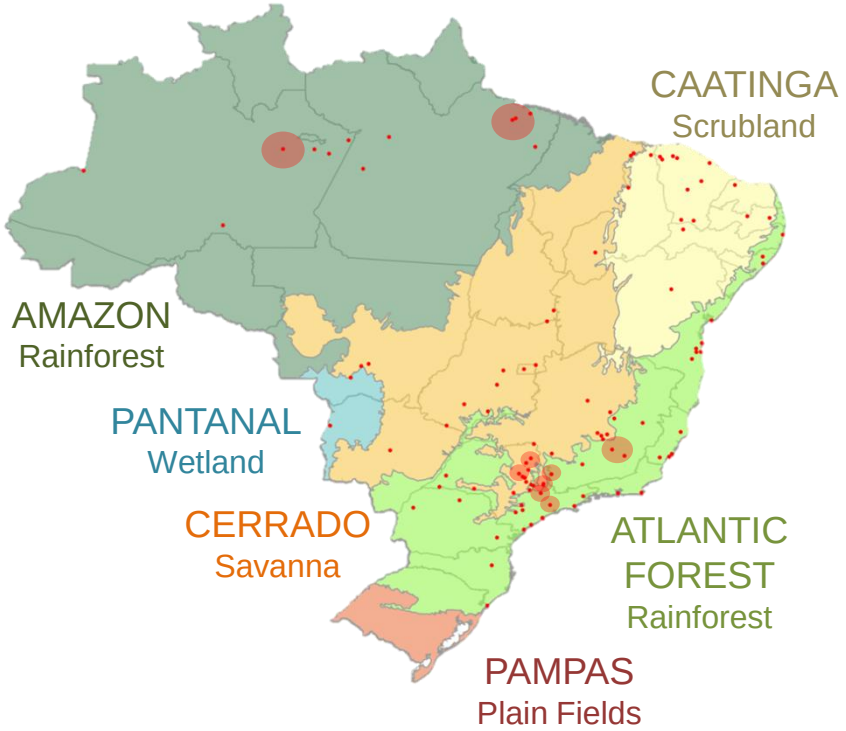
NuBBE Database

Version 2.0

2219 compounds



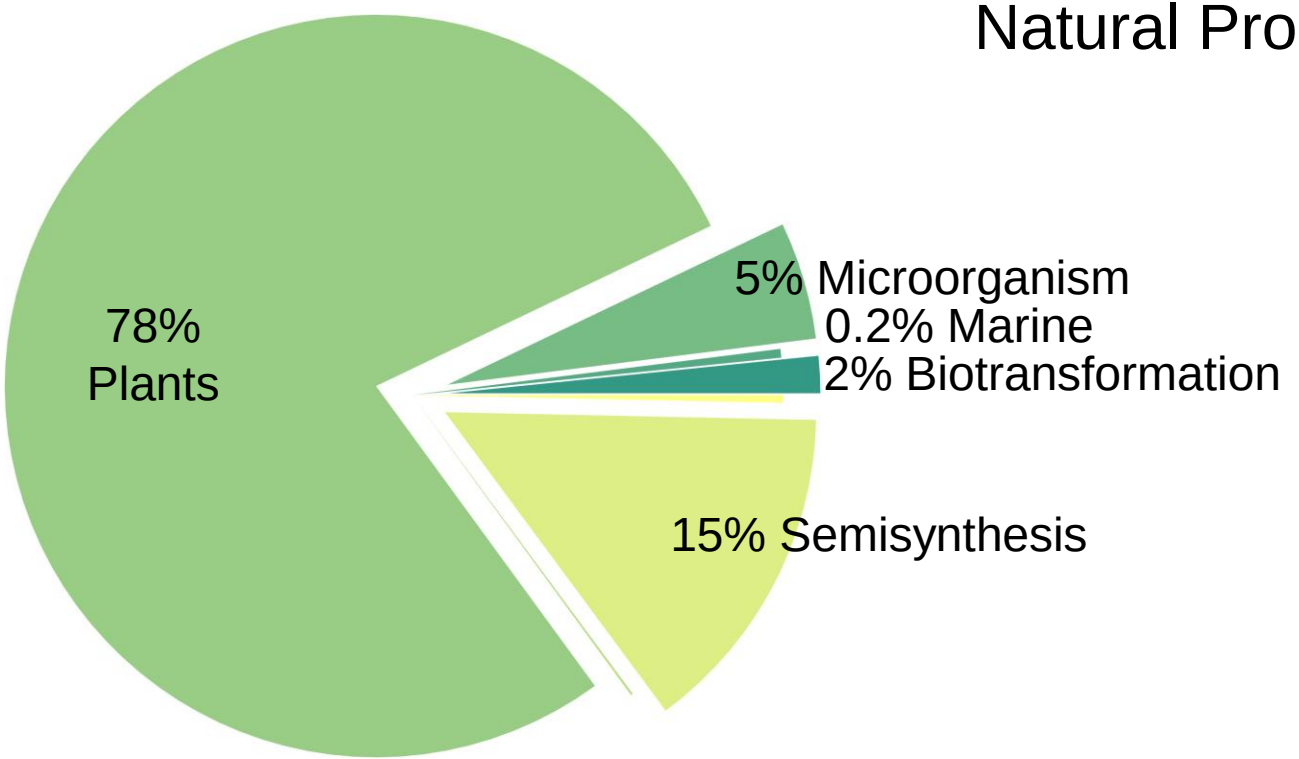
Number of Occurrences per State



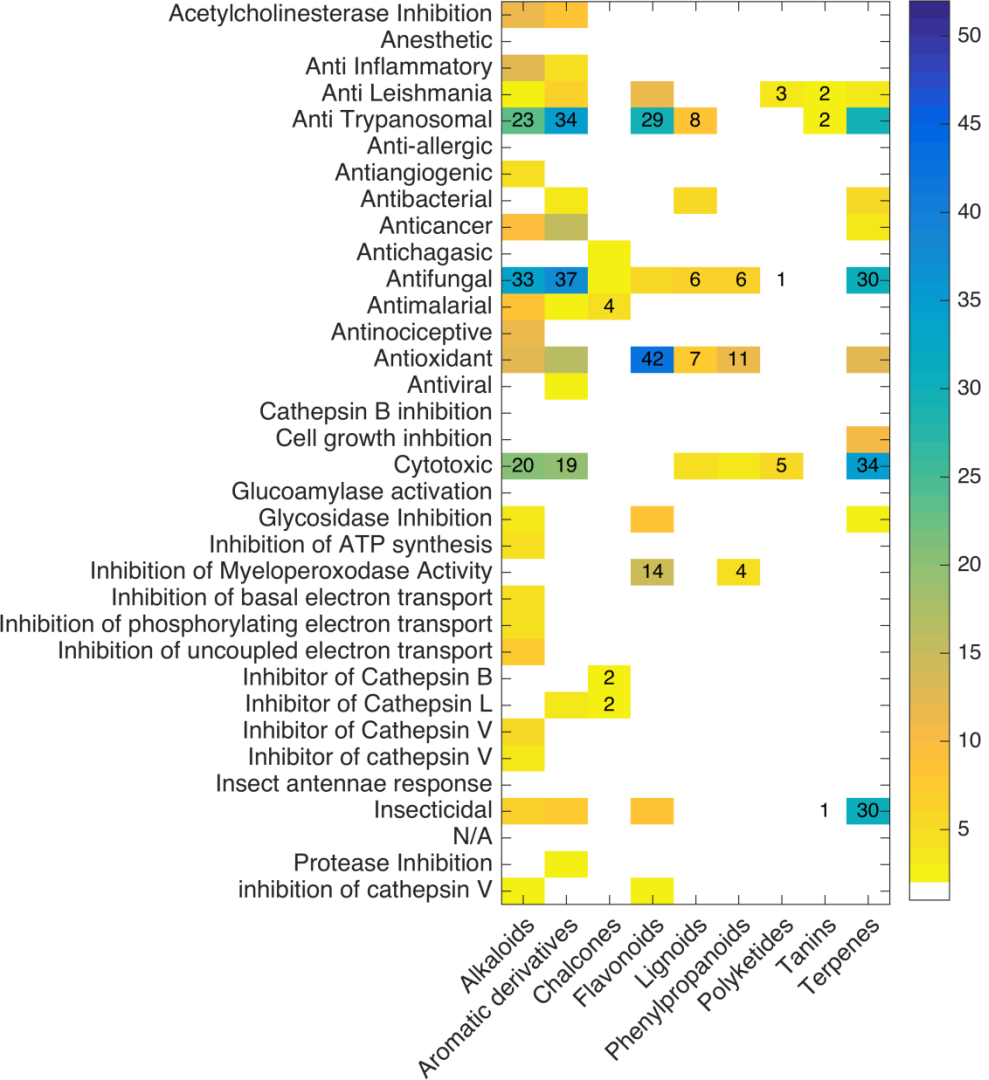
Distribution per Biome

Pilon, A.C. et al. Scientific reports. 7:7215, 2017

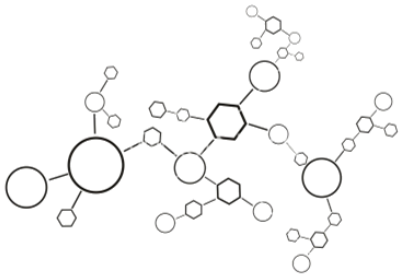
Main sources of Brazilian Natural Products



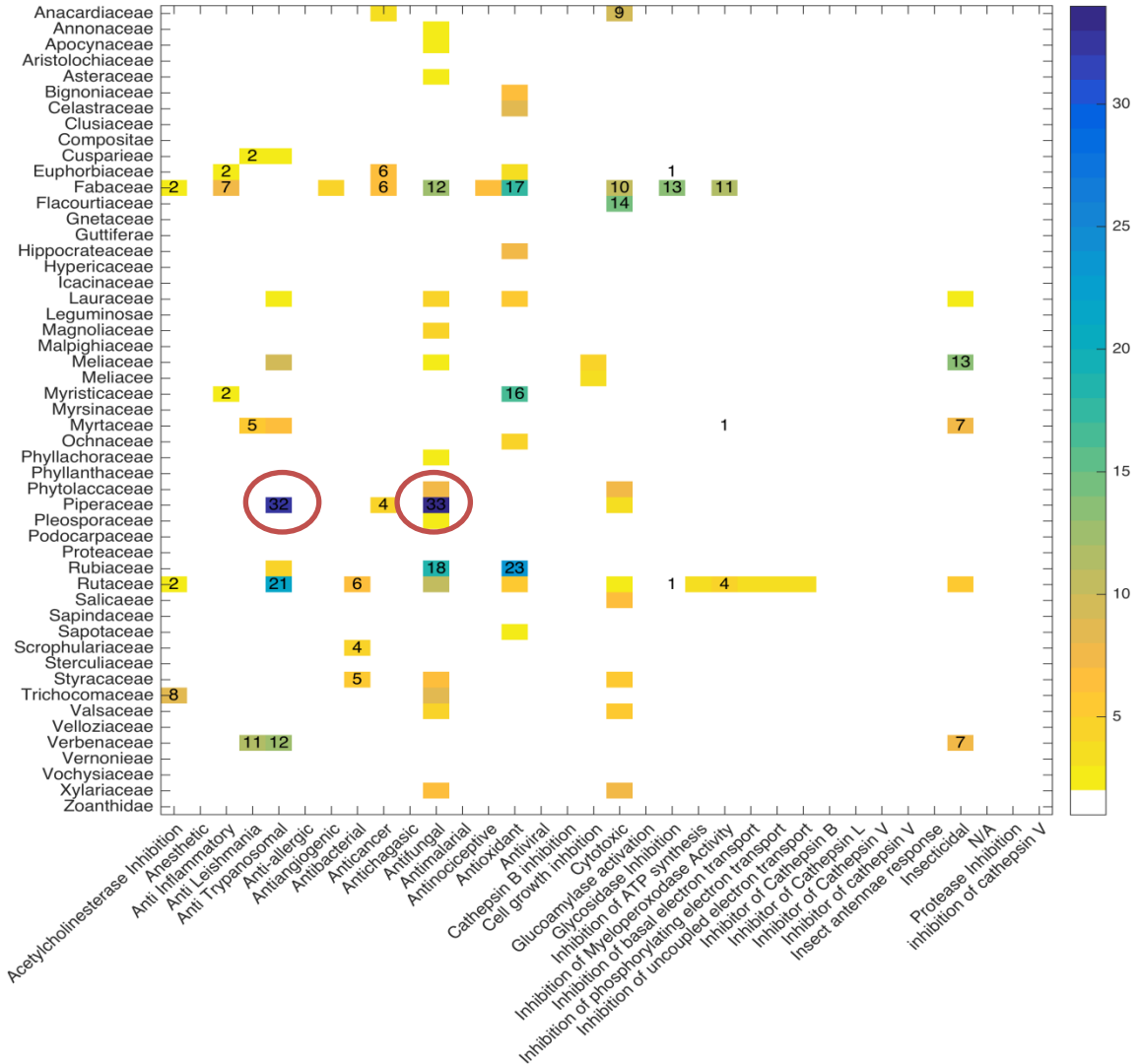
Correlations between Metabolite Classes and biological Activity



Alkaloids
Terpenes
Flavonoids



Pilon, A.C. et al. Scientific reports. 7:7215, 2017



Family X Biological Activity

Pilon, A.C. et al. Scientific reports. 7:7215, 2017

NuBBE Database

The Natural Products Database from Brazilian Biodiversity

2010

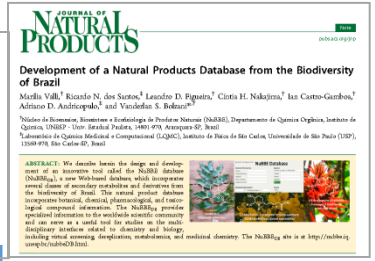
Start of 1st stage of the $NuBBE_{DB}$ project

FAPESP

2012

640 compounds were included, all identified by the research group NuBBE

First scientific paper about $NuBBE_{DB}$
Launch of the website



2013

2014

Inclusion of tools
- Automatic generation of Mol2
- Structure editor added to inclusion platform

molinspiration cheminformatics

ChemAxon Marvin

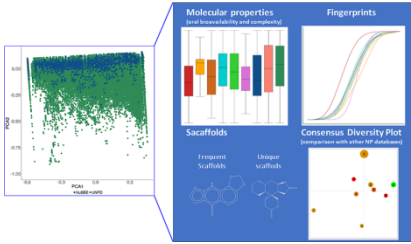
2015

Start of 2st stage of the project

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

Valli et al. J. Nat. Prod. 76(3), 439–444, 2013

Timeline of NuBBE Database project



www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

NuBBE$_{DB}$: an updated database to uncover chemical and biological information from Brazilian biodiversity

Received: 25 April 2017
Accepted: 28 June 2017
Published online: 03 August 2017

Alan C. Pilon[1], Marilia Valli[2], Alessandra C. Dametto[1], Meri Emili F. Pinto[1], Rafael T. Freire[1], Ian Castro-Gamboa[2], Adriano D. Andricopulo[2] & Vanderlan S. Bolzani[1]

2016

- website redesigned
- Inclusion of NMR data with ACD/Labs
- 1579 new entries

ACD/Labs

2017

Updated NuBBE$_{DB}$ for Brazilian Biodivesity

2019

Chemical Space and Diversity of the NuBBE$_{DB}$

2020

Start of 3rd stage of the project NuBBE$_{DB}$
Collaboration with CAS/ACS to increase content

Pilon; Valli et al. Scientific reports. 7:7215, 2017
Saldívar-González et al. J. Chem. Inf. Model. 59, 74-85, 2019

CAS
A DIVISION OF THE AMERICAN CHEMICAL SOCIETY

FAPESP

Collaborations

Collaboration with CAS/ACS to increase content

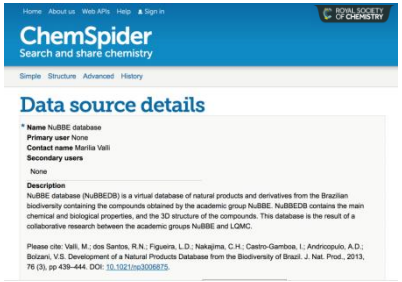
CAS
A DIVISION OF THE AMERICAN CHEMICAL SOCIETY

32,524 papers CNPq → 10,173 papers with DOI in CAPLUS → 51,973 compounds sdf file

ACD/Labs provides free NMR prediction tool

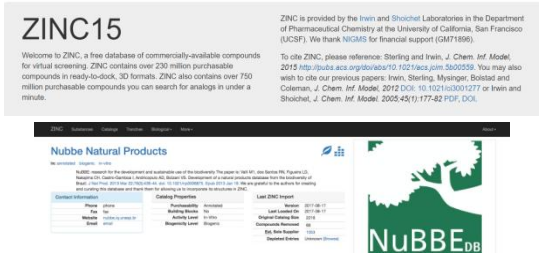
ACD/Labs

Collaborations to share content



http://www.chemspider.com/DatasourceDetails.aspx?id=806

http://zinc.docking.org/catalogs/nubbenp



Project Phase 3

Collaboration with CAS/ACS to increase content

32,524 Document references from CNPq

13,268 References With DOI

10,173 Documents found in CAPLUS

51,973 compounds curated by CAS

FAPESP

CAS
A DIVISION OF THE AMERICAN CHEMICAL SOCIETY

JOURNAL OF NATURAL PRODUCTS

Note

pubs.acs.org/jnp

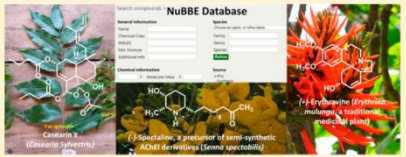
Development of a Natural Products Database from the Biodiversity of Brazil

Marilia Valli,[†] Ricardo N. dos Santos,[‡] Leandro D. Figueira,[†] Cíntia H. Nakajima,[†] Ian Castro-Gamboa,[†] Adriano D. Andricopulo,[‡] and Vanderlan S. Bolzani*[,†]

[†]Núcleo de Bioensaios, Biossíntese e Ecofisiologia de Produtos Naturais (NuBBE), Departamento de Química Orgânica, Instituto de Química, UNESP - Univ. Estadual Paulista, 14801-970, Araraquara-SP, Brazil

[‡]Laboratório de Química Medicinal e Computacional (LQMC), Instituto de Física de São Carlos, Universidade de São Paulo (USP), 13560-970, São Carlos-SP, Brazil

ABSTRACT: We describe herein the design and development of an innovative tool called the NuBBE database ($NuBBE_{DB}$), a new Web-based database, which incorporates several classes of secondary metabolites and derivatives from the biodiversity of Brazil. This natural product database incorporates botanical, chemical, pharmacological, and toxicological compound information. The $NuBBE_{DB}$ provides specialized information to the worldwide scientific community and can serve as a useful tool for studies on the multidisciplinary interfaces related to chemistry and biology, including virtual screening, dereplication, metabolomics, and medicinal chemistry. The $NuBBE_{DB}$ site is at http://nubbe.iq.unesp.br/nubbeDB.html.



Natural products have been a wonderful source of inspiration for the design and development of new drugs.[1−6] An inspection of drug approvals reveals that approximately 64% of all drugs considered had a natural

conservation initiatives with a solid scientific basis can be achieved.[12] Notable NuBBE research-related compounds include the *Casearia sylvestris*-derived cytotoxic clerodane diterpene casearin X,[13] the anxiolytic Erythrina alkaloid

***J. Nat. Prod.*, *76*, 439–444, 2013**

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

$NuBBE_{DB}$: an updated database to uncover chemical and biological information from Brazilian biodiversity

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Alan C. Pilon[1], Marilia Valli[1], Alessandra C. Dametto[1], Meri Emili F. Pinto[1], Rafael T. Freire[2], Ian Castro-Gamboa[1], Adriano D. Andricopulo[3] & Vanderlan S. Bolzani[1]

The intrinsic value of biodiversity extends beyond species diversity, genetic heritage, ecosystem variability and ecological services, such as climate regulation, water quality, nutrient cycling and the provision of reproductive habitats it is also an inexhaustible source of molecules and products beneficial to human well-being. To uncover the chemistry of Brazilian natural products, the Nuclei of Bioassays, Ecophysiology and Biosynthesis of Natural Products Database ($NuBBE_{DB}$) was created as the first natural product library from Brazilian biodiversity. Since its launch in 2013, the $NuBBE_{DB}$ has proven to be an important resource for new drug design and dereplication studies. Consequently, continuous efforts have been made to expand its contents and include a greater diversity of natural sources to establish it as a comprehensive compendium of available biogeochemical information about Brazilian biodiversity. The content in the $NuBBE_{DB}$ is freely accessible online (https://nubbe.iq.unesp.br/portal/nubbedb.html) and provides validated multidisciplinary information, chemical descriptors, species sources, geographic locations, spectroscopic data (NMR) and pharmacological properties. Herein, we report the latest advancements concerning the interface, content and functionality of the $NuBBE_{DB}$. We also present a preliminary study on the current profile of the compounds present in Brazilian territory.

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More information: Dr. Marilia Valli - marilia.valli@ifsc.usp.br

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marilia.valli@ifsc.usp.br

NuBBE

LQMC Laboratório de Química Medicinal e Computacional

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

FAPESP

USP

unesp

CIBFar

INCT BioNat Biodiversidade e Produtos Naturais

DIFACQUIM UNAM

DIFACQUIM COMPUTER-AIDED DRUG DESIGN AT UNAM

ChemSpider The free chemical database

molinspiration cheminformatics

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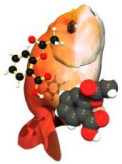

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