PRÓPOLIS:
from the bee hive to the clinic

Prof. Dr. Niraldo Paulino

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Prof. Niraldo Paulino
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Biochemical Pharmacist, Master and Doctor in Pharmacology from the Federal University of Santa Catarina and Maximilian Universität München (2005). Coordinator of the Biomedical Research and Development Group, in the Professional Master's Program in Pharmacy at UNIBAN (SP) (until 2016). Currently Technical-Scientific Advisor and Business Director at Medical Lex Ltda. Has experience in the area of Pharmacology, with emphasis on Biochemical and Molecular Pharmacology of Medicinal Plants. Acting mainly on the themes: Mechanism of action of Medicinal Plants and Natural Products, Inflammation and its pharmacodynamic mechanisms.

Bee Products

***Apis mellifera* Linnaeus,1758**

honey, propolis, apitoxin, beeswax, royal jelly, pollen

Definition

Ministry of Agriculture of Brazil
Instrução Normativa SDA Nº 03, de 19-01-2001

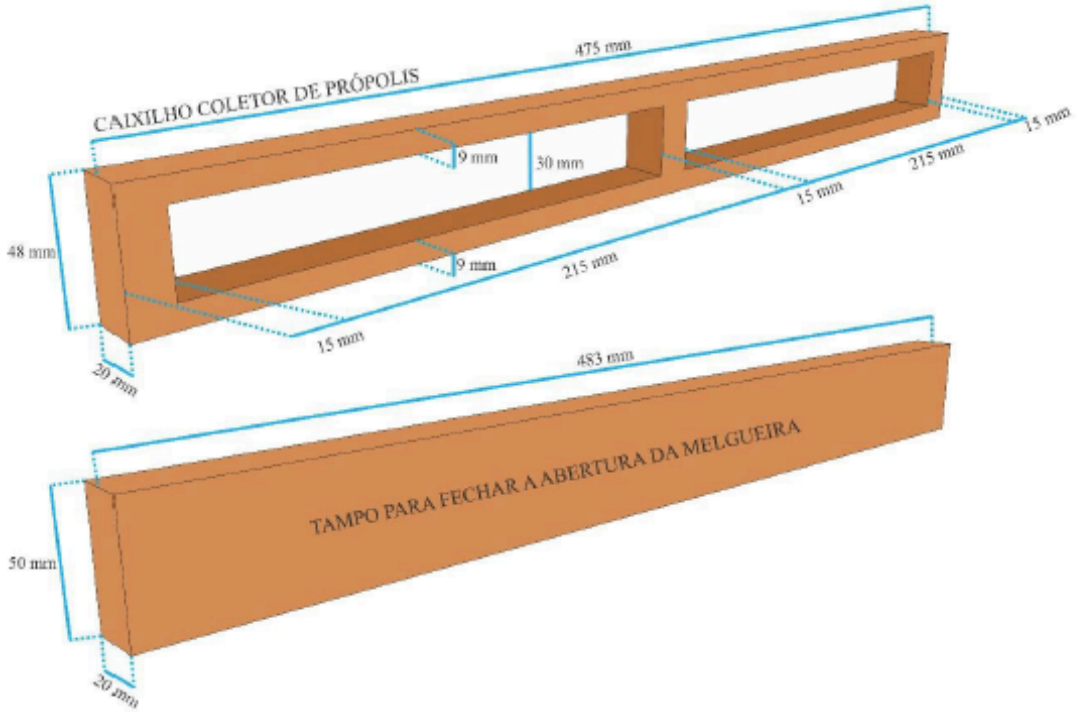
Definition: Propolis is a product derived from resinous, gummy and balsamic substances, collected by bees, from shoots, flowers and exudates from plants, in which bees add salivary secretions, wax and pollen for the final preparation of the product.

from the bee hive
to the clinic

Propolis production

Lateral openings in the melgueras with insertion of mobile frame (propolis frame)
This is the most recommended collector.
Advantage:
- Low cost and easy to use;
- Better protection and quality of propolis, since the propolyzed side of the collector is oriented towards the inside of the hive;
- The propolis boxes can be removed and replaced without opening the hive and with little use of smoke;

Propolis production



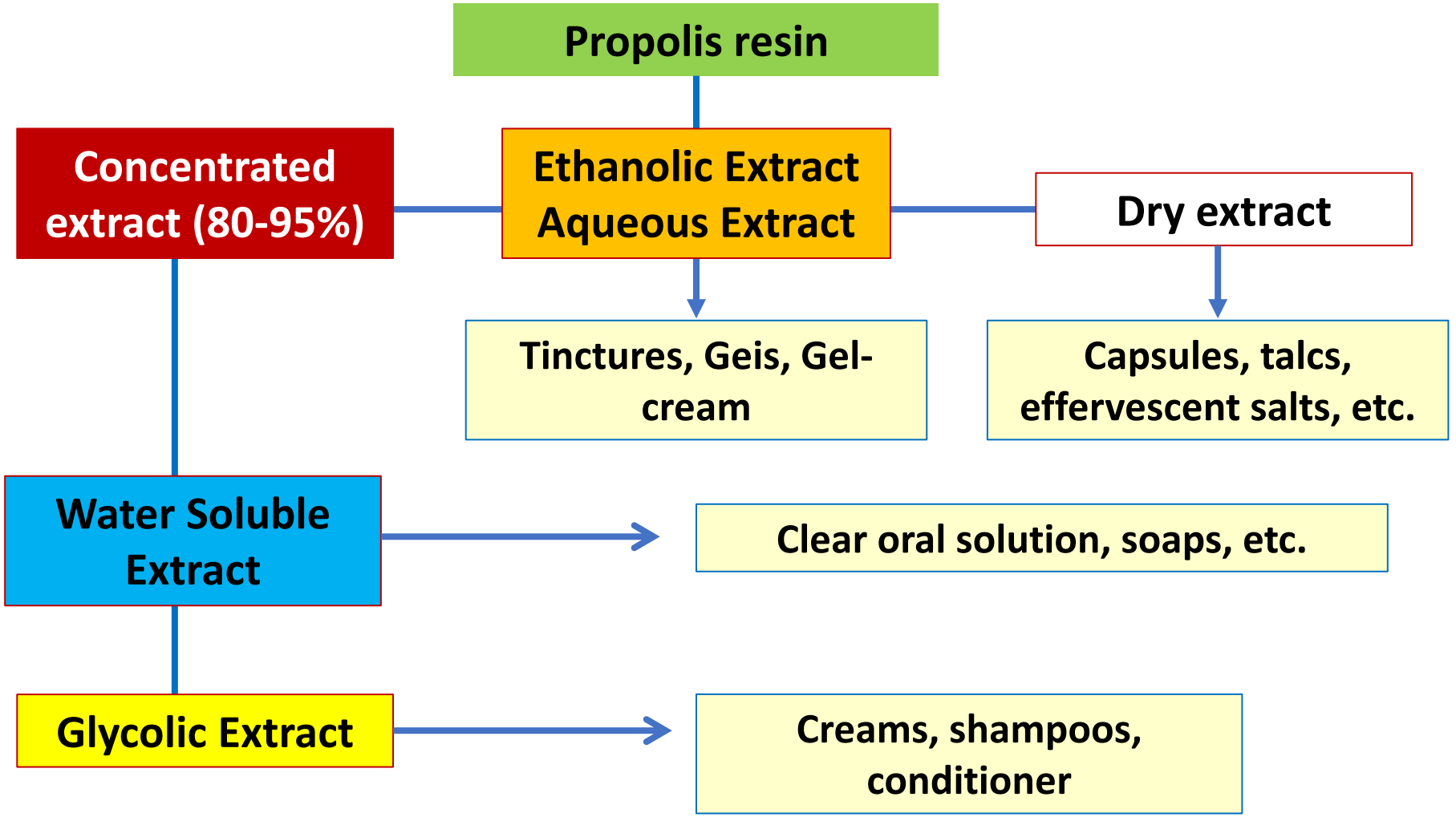
Propolis production





Production and collection for transport to the apiary

Propolis Extracts



Propolis Extracts

Propolis resin

Ethanolic Extract

Propolis extracts

Concentrated extract (80-95%) — **Ethanolic Extract**

To obtain the soft extract, the solvent evaporation process will be used in rotary evaporation equipment or by simple evaporation with a temperature between 40-50C until the thick consistency of the extract with the smallest possible volume of solvent. In general, a concentration of around 90% or more is achieved in this extract.

Propolis extracts

Water Soluble Extract — **Concentrated extract (80-95%)**

To obtain the water-soluble extract of propolis, the process of mixing a desired amount of soft extract to a fraction of Cremophor RH40 will be used until obtaining a homogeneous mass. Then and little by little add water, always mixing well for the total emulsification of the desired volume.

Cremophor® RH 40

INCI Name:

PEG-40 Hydrogenated Castor Oil

Empresa:

BASF Latin America

Cremophor® RH 40 is a non-ionic solubilizer and emulsifying agents obtained by reacting hydrogenated castor oil with ethylene oxide. The main components of the product are glyceryl polyethylene glycol oxystearate, which, together with fatty acid esters of polyglyceryl glyceryl, form the hydrophobic part of the product. Cremophor® RH 40 is used to solubilize ethereal oils, perfume compositions, vitamins and hydrophobic active substances in aqueous-alcoholic and purely aqueous solutions.

Propolis extracts

Glycolic Extract — **Water Soluble Extract**

To obtain the glycolic extract of propolis, the process of mixing a desired amount of water-soluble extract with known concentration will be used and it is diluted with propylene glycol until the desired volume of glycolic extract is obtained.

It is also possible to obtain the glycolic extract of propolis, using the process of mixing a desired quantity of soft extract to a fraction of Cremophor RH40 until obtaining a homogeneous mass. Then, little by little, add propylene glycol, always mixing well for the total emulsification of the desired volume.

Cremophor® RH 40

INCI Name:

PEG-40 Hydrogenated Castor Oil

Propolis extracts

Dry extract — **Ethanolic Extract**

To obtain the dry extract of propolis, the process of mixing a desired amount of ethanol extract with known concentration will be used and a proportion of talc or avicel is added until the homogeneous incorporation of the extract in the powder mixture. Then proceed to sieving to standardize the granulometry and final drying.

It is also possible to obtain the dry extract from the freeze-drying of the propolis extract or atomization until obtaining the pulverized concentrate.

Avicel is a microcrystalline cellulose powder that is used in both the food and pharmaceutical industries.

Liofilizador de bancada L101

Propolis Dry Extract

Pharmaceutical and cosmetic products

Tinctures, Geis, Gel-cream

Capsules, talcs, effervescent salts, etc.

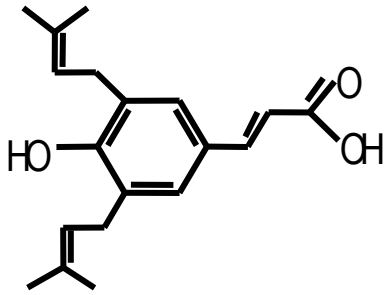
Clear oral solution, soaps, etc.

Creams, shampoos, conditioner

Pharmaceutical grade propolis

Propolis

Botanical Sources	Chemistry	Activities	Manufacturer
Plant sources with propolinizing resins and phyto-geographic variations for occurrences of propolis types	Description of the main biological compounds described in Brazilian propolis	Biological activities described in the literature and proposed therapeutic uses based on scientific evidence in vivo, in vitro and clinical.	Description and legal data of the manufacturer, registration bodies, responsible pharmacist and quality certification.



Anti-inflammatory
Antitumor
Antioxidant
Antibacterial
Antimycotics
Antiviral
Immunomodulatory

MINISTÉRIO DA AGRICULTURA
BRASIL
INSPECIONADO
3005
S.I.F.

Green Propolis

Bees collect resinous substances from certain plants

These substances are transformed into the hive and used to close the opening and protect it from the proliferation of bacteria, fungi and viruses.

This resinous substance is called propolis.

Propolis is collected, cleaned, crushed and percolated under standardized conditions (usually in alcohol) to produce extract.

Propolis extract is used to prepare various pharmaceutical formulations: capsules, creams, oral spray, shampoos ...

Green Propolis

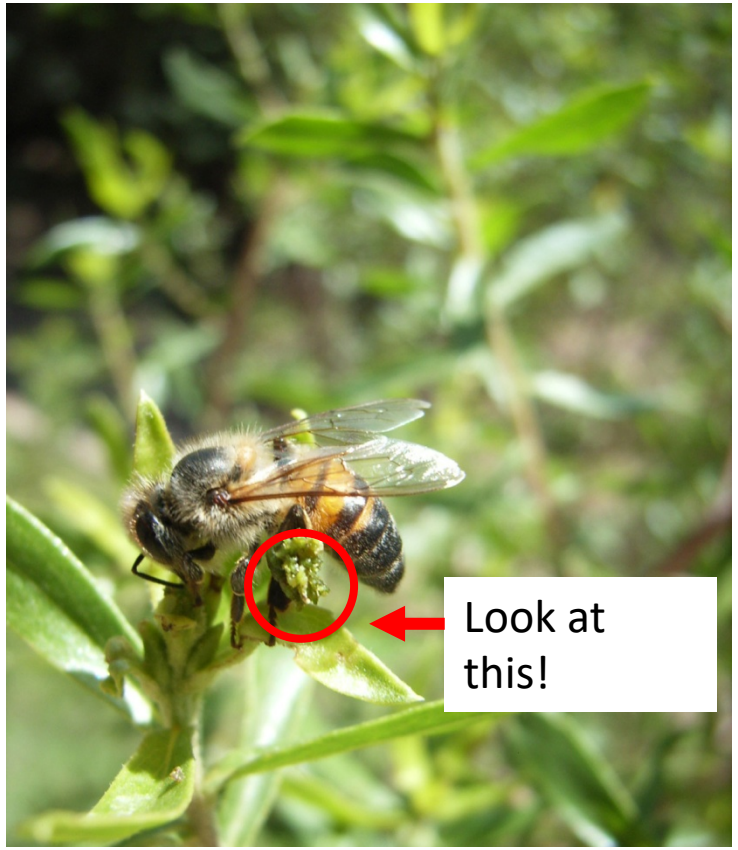
Climatic and vegetation conditions also contribute to this type of production. The state of Minas Gerais alone produces 29 tons of propolis, being responsible for 70% of the production in the whole of

Brazil, according to the Brazilian Micro and Small Business Support Service (Sebrae). In Brazil, the monthly production of green propolis is around 41 tons

Green

In Brazil we have many phytogeographic regions and many types of propolis (at least 14) with different chemical constitutions.

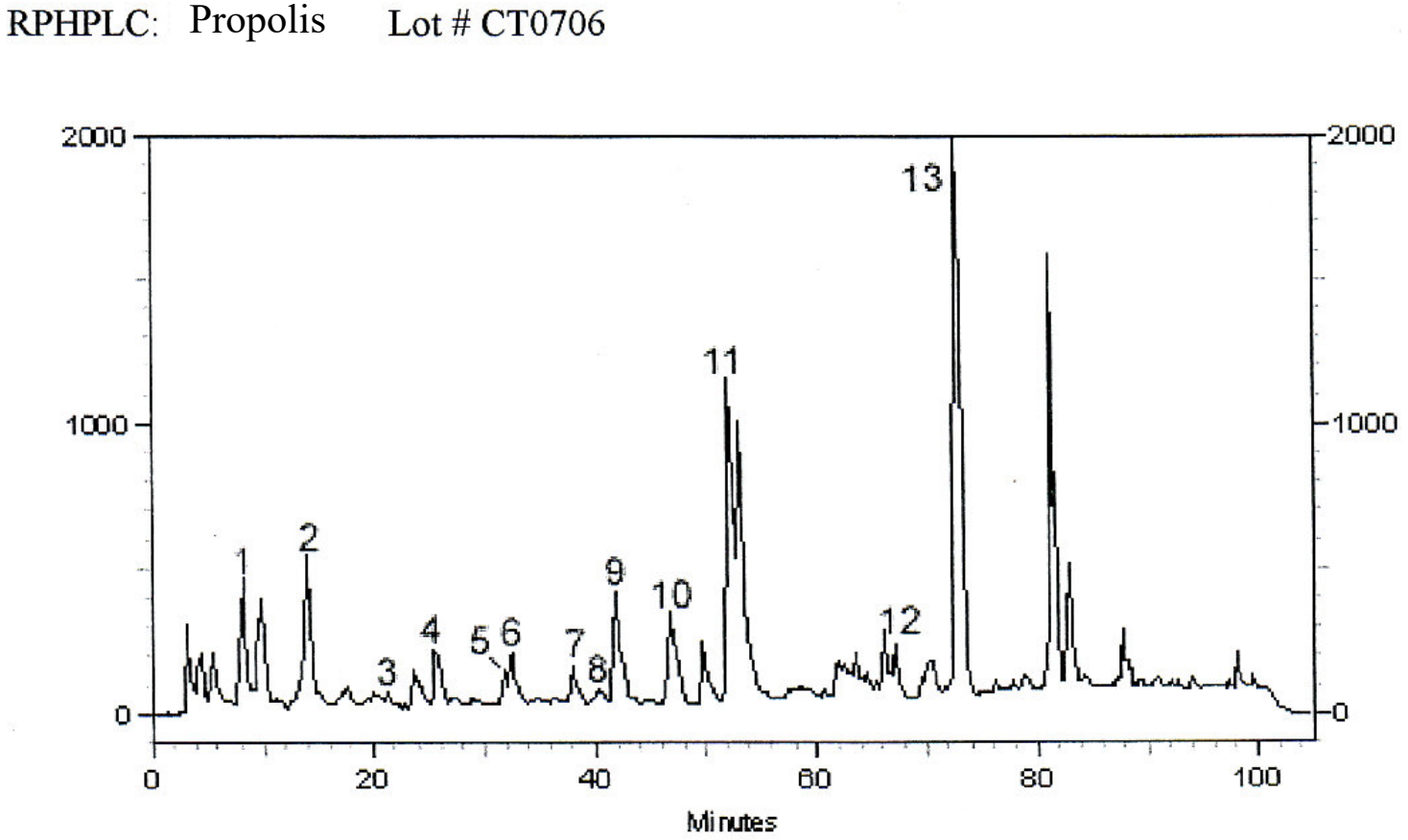
Green Propolis from *Baccharis dracunculifolia*



Bees collect a green resin from *Baccharis dracunculifolia.*

Beekeepers in operation to collect Baccharis propolis

Green Propolis from *B. dracunculifolia*



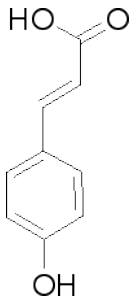
The chemical composition of *Baccharis dracunculifolia* propolis was determined by HPLC using a Merck-Hitachi equipment (Germany), equipped with a pump (model L-7100, Merck-Hitachi) and a diode detector (model L-7455, Merck-Hitachi). Phenolic compounds (mg / g) (1) coumaric acid (3.81), (2) rutin (9.87), (3) pinobanksin (3.48), (4) quercetin (2.15), (5) kaempferol (0.78), (6) apigenin (1.86), (7) pinocembrin (22.55), (8) pinobanksin-3-acetate (4.10), (9) chrysin (2.49), (10) galangin (4.14), (11) kaempferide (5.59) , (12) tectochrysin (2.90), (13) ARTEPILLIN C (87.97).

Green Propolis from *B. dracunculifolia*

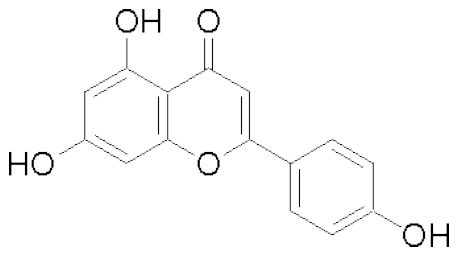
Peak	Name	Retention time	Content (mg/g)
1	Coumaric acid	8.176	3.81
2	Rutin	14.058	9.87
3	Pinobanksin	21.209	3.48
4	Quercetin	25.598	2.15
5	Kaempferol	31.946	0.78
6	Apigenin	32.611	1.86
7	Pinocembrin	38.083	22.55
8	Pinobanksin-3-acetate	40.200	4.10
9	Chrysin	41.792	2.49
10	Galangin	46.789	4.14
11	Kaempferide	52.137	5.59
12	Tectochrysin	67.054	2.90
13	Artepillin C	72.599	87.97

Chemical markers present in the propolis of *Baccharis dracunculifolia*

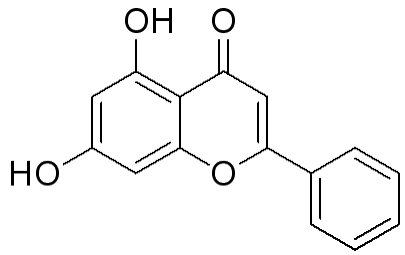
Common compounds in green propolis



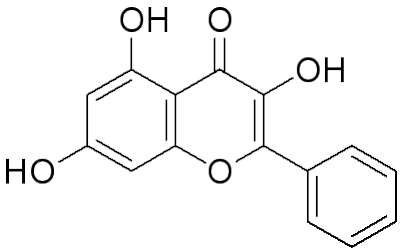
Coumaric acid



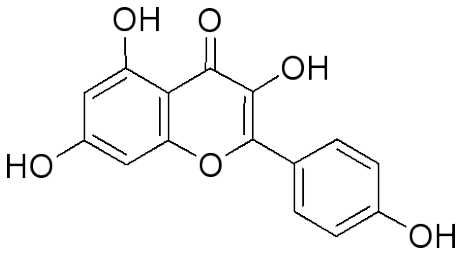
Apigenin



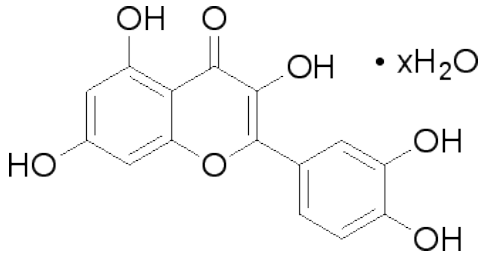
Chrisin



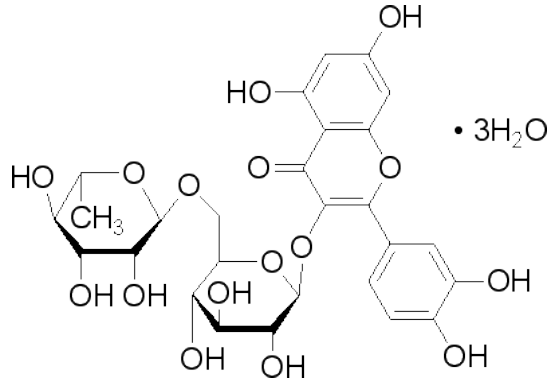
Galangin



Kaempferol

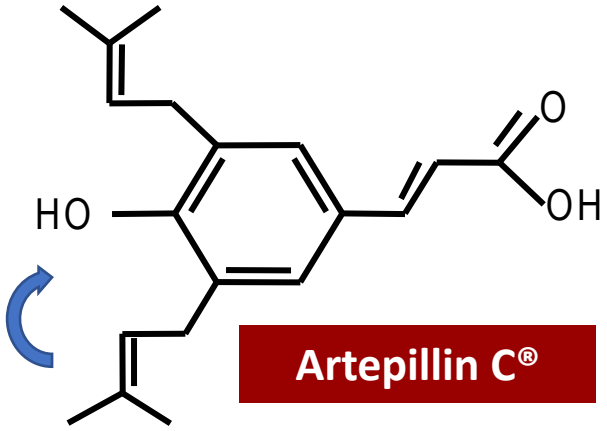


Quercetin

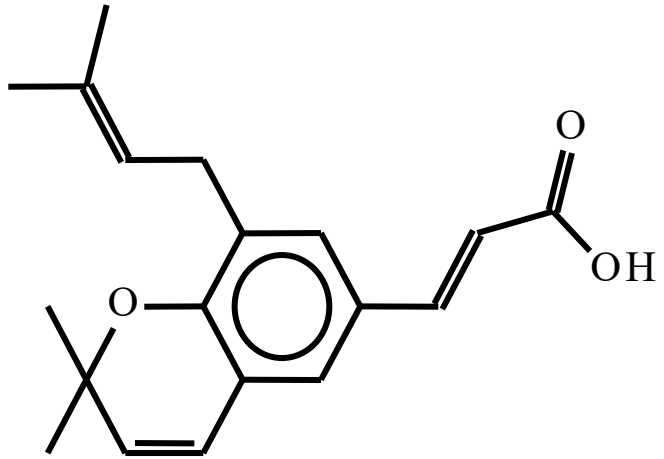


Rutin

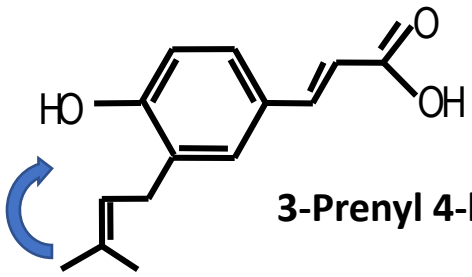
Unique compounds in green propolis



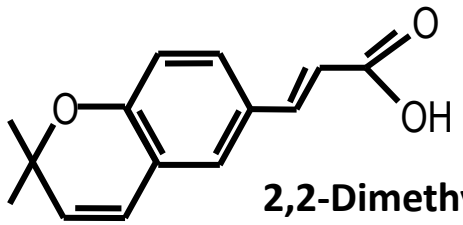
Artepillin C®



2,2-Dimethyl-6-carboxyethyl-8-prenyl-2H-1-benzopyran



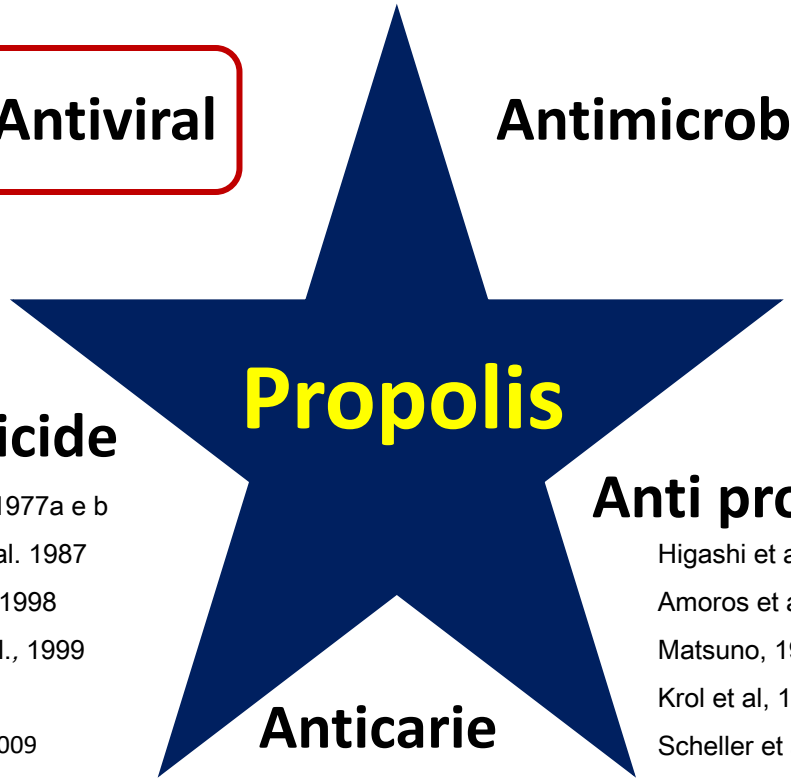
3-Prenyl 4-hydroxycinnamic acid



2,2-Dimethyl-6-carboxyethyl-2H-1-benzopyran

Prenylated compounds derived from cinnamic acid characteristic of green propolis and highly bioactive

Propolis



Antiviral

Debiaggi,1990
Schimidt, 1996
Burdock, 1998
Scheller et al.,1998
Kujumgiev et al., 1999
Vynograd et al., 2000
Huleihel e Isanu, 2002
Abd Al Hady et al., 2003
Ilhan et al., 2004
Sartori et al., 2012
Búfalo et al., 2009
Shimizu et al., 2012
Yildirim A et al., 2016
Silva-Beltrán NP et al., 2019
Labská K et al., 2018
González-Búrquez MJ et al., 2018
Altındiş M et al., 2020
Kitamura H et al., 2018
Governa P, et al., 2019

Antimicrobial

Grange et al, 1990
Aga et al., 1994
Kain et al., 1996
Kujumgiev et al., 1999
Kartal et al., 2003
Santos et al., 2003
Ugur e Arsian 2004
Morawiec et al., 2015
Bueno Silva et al., 2016
Machado et al., 2016
Fiordalise et al., 2016
Freires et al., 2016
Veiga et al., 2017
Soares et al., 2017

Fungicide

Scheller et al.,1977a e b
Millet-Clerc et al. 1987
Scheller et al., 1998
Kujumgiev et al., 1999
Ozean 2004
Siqueira et al., 2009
Dota et al., 2011
Ngatu et al., 2012
Freires et al., 2016
Pippi et al., 2016

Anti protozoan

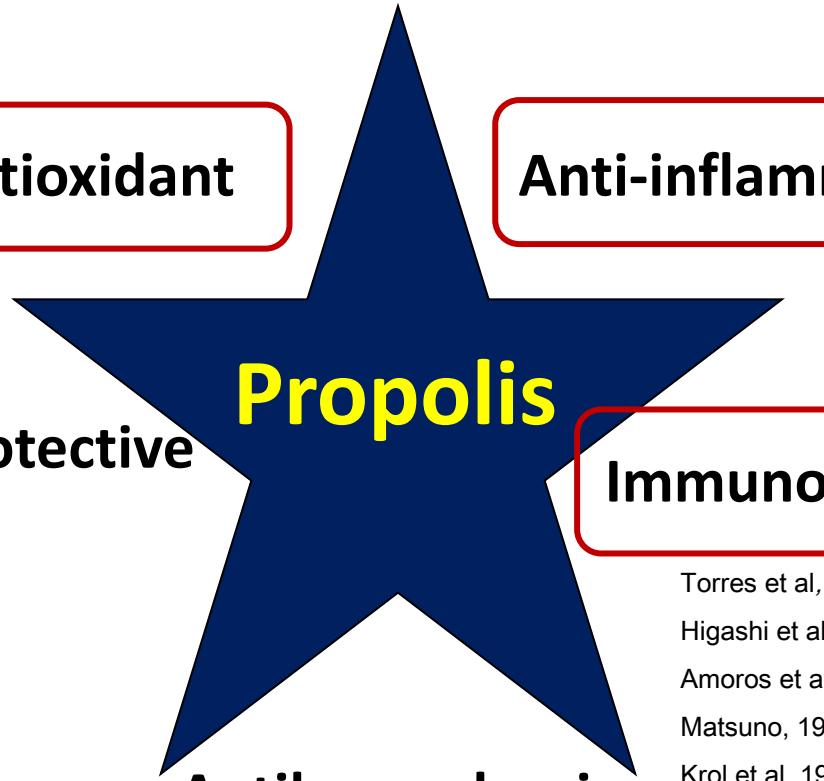
Higashi et al, 1991
Amoros et al., 1992a, 1992b
Matsuno, 1992
Krol et al, 1993
Scheller et al 1998
da Silva Filho et al., 2004
da Silva Cunha et al., 2004
Santana et al., 2014
Otoguro et al., 2012

Anticarie

Ikeno et al., 1991
Steinberg et al., 1996
Botushanov et al., 2004
Bretz et al., 2014
Anauate-Netto et al., 2013, 2014

3.331 results

Propolis



Antioxidant

Krol et al., 1990
Scheller et al., 1990
Dobrowolski et al., 1991
Schmidt, 1996
Volpert e Elstner, 1996
Ichikawa et al., 2002
Shinohara et al., 2002
Simões et al., 2004
Shimizu et al., 2004
De Mendonça et al., 2015
Machado et al., 2015
Zhao et al., 2016
Veiga et al., 2017

Anti-inflammatory

Bankova et al.,1983
Wang et al., 1993
Khayyal et al., 1993
Schimidt, 1996
Volpert e Elstner, 1996
Mirzoeva e Calder, 1996
Menezes et al., 1999
Paulino et al., 2003
Silva et al., 2004
Paulino et al., 2006 a, b
Paulino et al., 2008
Paulino et al 2015
Paulino et al., 2016

Hepatoprotective

Merino et al., 1996
Basnet et al., 1996
Lin et al., 1997
Banskota et al., 2001
El-Khatib et al., 2002
Seo et al., 2003
Shukla et al., 2004
Liu et al., 2004
Paulino et al., 2014

Immunomodulatory

Torres et al, 1990
Higashi et al, 1991
Amoros et al., 1992a, 1992b
Matsuno, 1992
Krol et al, 1993
Scheller et al 1998
da Silva Filho et al., 2004
da Silva Cunha et al., 2004
Fischer et al., 2007 a, b
Fischer et. al 2010
Chan GC 2013
Al-Hariri M. 2019
Touzani S et al., 2019
Dos Santos Thomazelli APF 2017
Sena-Lopes Â 2018

Antihyperalgesic

Paintz e Metzer, 1979
Schimidt, 1996
Paulino et al.,1996d
Campos et al., 1998
Paulino et al., 2003

Propolis

ANTITUMORAL

Da Silva et al, 2016
Kakehashi et al., 2016
Nguyen et al., 2016
De Mendonça et al., 2015
Frión-Herrera et al., 2015
Begnini et al., 2014
Ishiai et al., 2014
Munari et al., 2014
De Oliveira et al., 2014
Pinheiro et al., 2014
Ishikawa et al., 2012
Cinegaglia et al., 2013
Kamiya et al., 2012

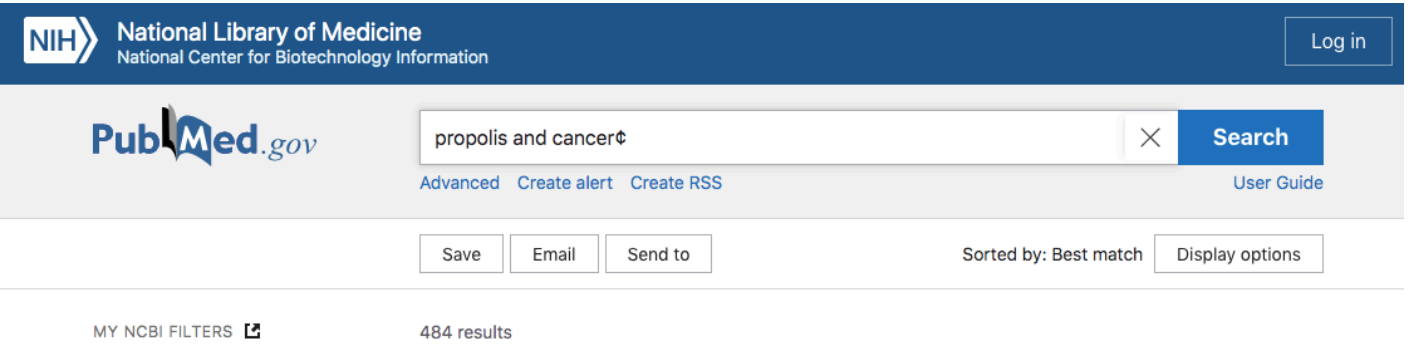
E muitos otros.....

484 results

Propóleo

ANTITUMORAL

Ribeiro et al. 2006
Padmavathi et al., 2006a
Scifo et al., 2006
Chen et al., 2006
Bestwick et al., 2006
Padmavathi et al., 2006b
Padmavathi etal., 2006c
Chen et al., 2005
Abdel-Latif et al., 2005
Shimizu et al., 2005a
Shimizu et al., 2005b
Hwang et al., 2006
Orsolic et al., 2005a
Orsolic et al., 2005b
Gunduz et al., 2005
Orsolic et al., 2005c
Jin et al., 2005
Mishima et al., 2005
Kuo et al., 2006
Weng et al., 2005
Shieh et al., 2005
Orsolic et al., 2005
Woo et al., 2005
Lee et al., 2004
De Lima et al., 2005
Russo et al., 2004
Woo et al., 2004
Scifo et al., 2004
Kumazawa et al., 2004
Aso et al., 2004
Orsolic et al., 2003
Shimizu et al., 2004
Gambelunghe et al., 2003
Liao et al., 2003
Chen et al., 2004
Lee et al., 2003
Asao et al., 2003
Chen et al., 2003
Sugimoto et al., 2003
Kimono et al., 2001a
Kimoto et al., 2001b
Kimono et al., 2000
Kimono et al., 1998
Kimoto et al., 1996
Scheller et al., 1989



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Systematic scientific study for verticalization of technology transfer and innovation for the industry

Systematic study for the pharmaceutical development of Brazilian propolis

1999

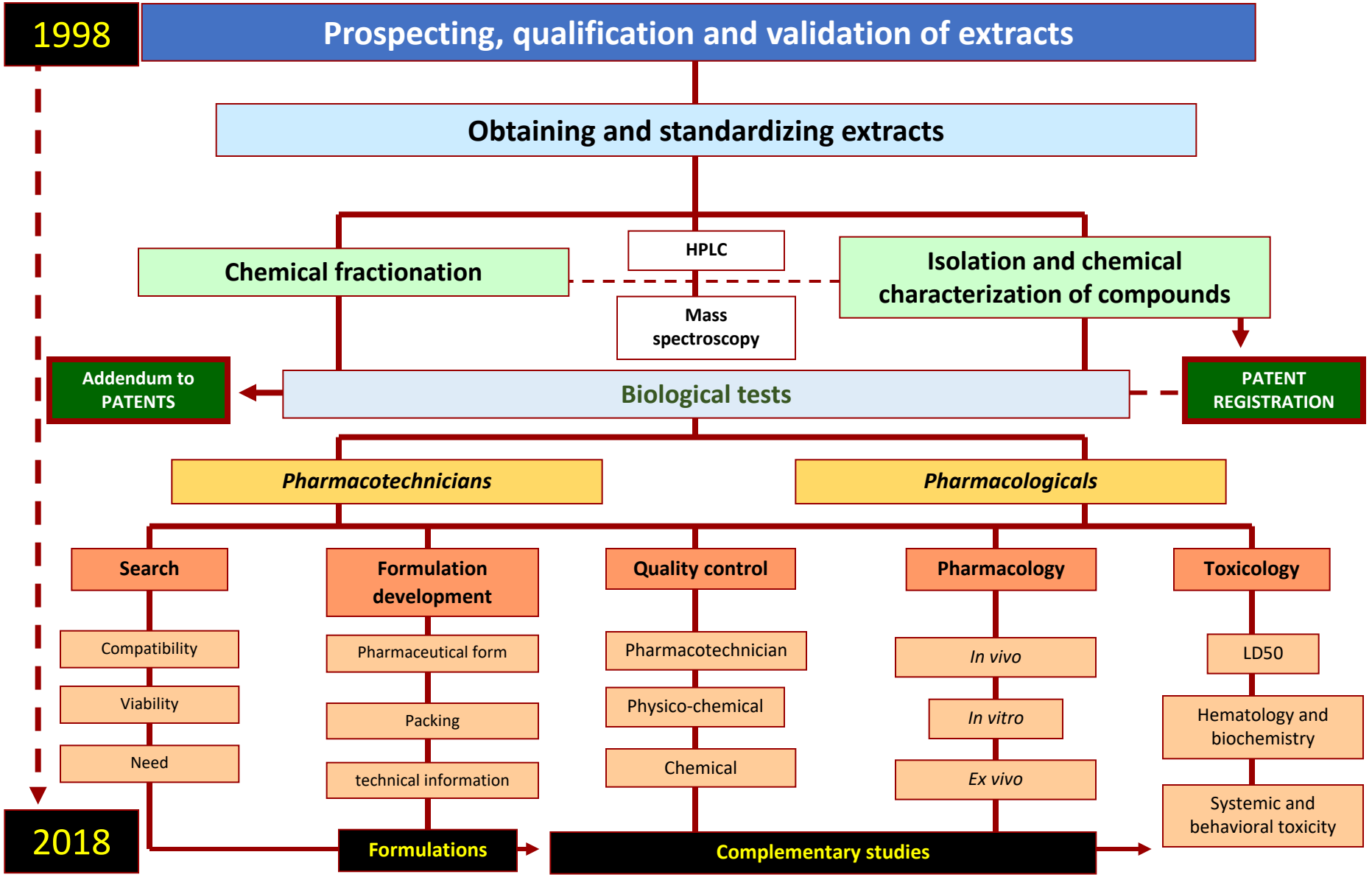
Systematic study for the pharmaceutical development of Brazilian propolis

1998

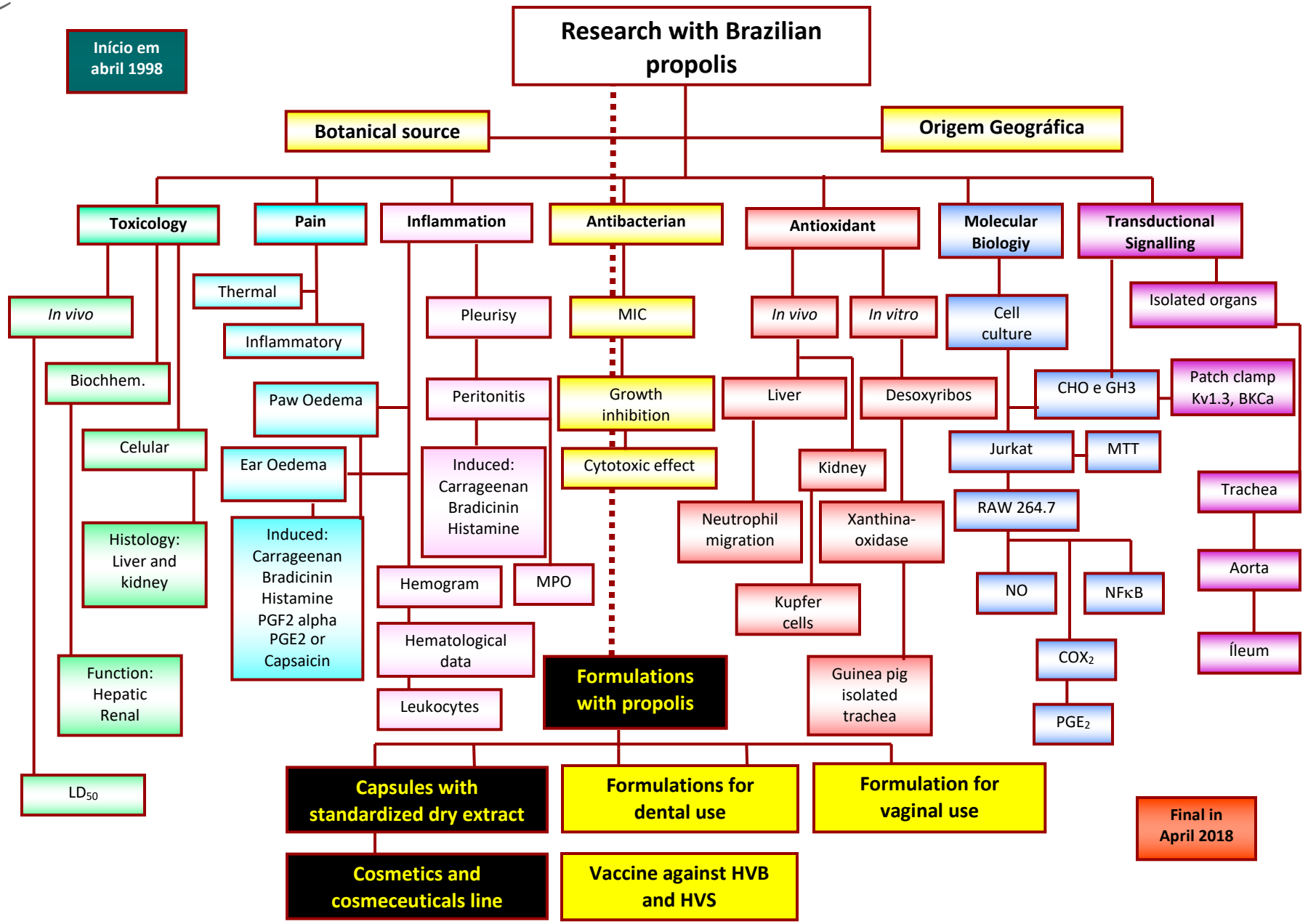
Two major partners in the industry for the systematic study of Brazilian propolis

Pharma Nectar

Brazilian Propolis Study



Brazilian Propolis Study



Brazilian Propolis Study

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Propolis from Brazil

Brazilian universities

UNIBAN
UNIVERSIDADE BANDEIRANTE DE SÃO PAULO

foreign universities

LMU Ludwig-Maximilians-Universität München

DAAD Deutscher Akademischer Austausch Dienst
German Academic Exchange Service

THE UNIVERSITY OF TOKUSHIMA

financial support

FINEP
FINANCIADORA DE ESTUDOS E PROJETOS
MINISTÉRIO DA CIÊNCIA E TECNOLOGIA

CNPq
Conselho Nacional de Desenvolvimento Científico e Tecnológico

FAPESP
FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO

FAPESC

Indústrias

ipi Institute of Pharmaceutical Innovation

Nature's Laboratory

BEEVITAL

James Fearnley
Nature's Laboratory Ltd
England - UK

Pharma Nectar

Néctar Farmácia Ltda
Belo Horizonte MG

Apis-Nativa Produtos
Naturais Ltda
Rua Caetano Lumertz, 49
Araranguá, SC

Typification of Brazilian Propolis

Prospecting, qualification and validation of extracts

Obtaining and standardizing extracts

Chemical fractionation

HPLC

Espectroscopia de massa

Isolation and chemical characterization of compounds

PATENT IN BRAZIL AND ABROAD

JOURNAL OF ETHNOPHARMACOLOGY
An Interdisciplinary Journal Devoted to Indigenous Drugs
The Official Journal of the International Society for Ethnopharmacology

MARCUCCI, M. C. ; FERRERES, F. ; GARCÍAVIGUERA, C. ; BANKOVA, V. S. ; CASTRO, S. L. ; DANTAS, A. P. ; VALENTE, P. H. M. ; PAULINO, N. . Phenolic compounds from Brazilian propolis with pharmacological activities.. Journal of Ethnopharmacology, Estados Unidos, v. 74, p. 105-112, 2001

Work that depicts four compounds found in Brazilian propolis: (1) 3-prenyl-4-hydroxycinnamic acid ,, (2) 2,2-dimethyl-6-carboxyethenyl-2H-1-benzopyrane, (3) 3,5-diprenyl -4-hydroxycinnamic acid and (4) 2,2-dimethyl-6-carboxyethenyl-8-prenyl-2H-1-benzopyran.

Patents submitted for the Brazilian Propolis Typification

Título – TYPING NATURAL PRODUCTS
País – Japão (PCT)
Descrição – Número do pedido: 2002-552654. Data de depósito: 20/06/2003.
PCT/BR01/00159. Prioridade: 22/12/00.
Nome do depositante: Maria Cristina Marcucci Ribeiro.
Nome dos inventores: Maria Cristina Marcucci Ribeiro.
Nome do procurador: Beerre Assessoria Empresarial Ltda

Título – TYPING NATURAL PRODUCTS
País – Comunidade Européia (PCT)
Descrição – Número do depósito: EP 012719175. Data de depósito: 20/06/2003.
PCT/BR01/00159 Prioridade: 22/12/00.
Nome do depositante: Maria Cristina Marcucci Ribeiro.
Nome dos inventores: Maria Cristina Marcucci Ribeiro.
Nome do procurador: Beerre Assessoria Empresarial Ltda

Título – PROCESSO DE IDENTIFICAÇÃO DE TIPAGENS DA PRÓPOLIS BRASILEIRA
País – Brasil (INPI-Rio de Janeiro)
Descrição – Número do pedido: PI 0006272-3 Data de depósito: 22/12/2000, publicada em 16/08/2002.
Nome do depositante: Maria Cristina Marcucci Ribeiro (transferido para Fundação de Amparo à Pesquisa do Estado de São Paulo – Fapesp).
Nome dos inventores: Maria Cristina Marcucci Ribeiro.
Nome do procurador: Beerre Assessoria Empresarial Ltda

Biological Activities

Biological tests

Farmacológicos

JOURNAL OF PHARMACY AND PHARMACOLOGY
An international journal of pharmaceutical science
ISSN: 0022-3573

CAMPOS, R. O. P. ; **PAULINO, N.** ; SILVA, C. H. M. ; SCREMIN, A. ; CALIXTO, J. B. . Anti-hyperalgesic effect of the ethanolic extract of propolis. Journal of Pharmacy and Pharmacology, Inglaterra, v. 50, p. 1187-1193, 1998

The first studies with samples of standardized propolis from southern Brazil (P1), demonstrated antinociceptive activity in several models of pain in mice and rats, including nociception caused by acetic acid, kaolin and zimozan, as well as inhibition of both phases, neurogenic and persistent, from pain induced by formalin, or even pain induced by capsaicin (Campos et al., 1998).

Biological Activities

JOURNAL OF PHARMACY AND PHARMACOLOGY
An international journal of pharmaceutical science
ISSN: 0022-3573

PAULINO, N. ; SCREMIN, F. M. ; RAICHASKI, L. B. ; MARCUCCI, M. C. ; SCREMIN, A. ; CALIXTO, J. B. Mechanisms involved in the relaxant action of the ethanolic extract of propolis in the guinea pig trachea in vitro. Journal of Pharmacy and Pharmacology, Northern Ireland, v. 54, n. 6, p. 845-852, 2002.

We also demonstrated that Brazilian propolis produced a relaxing effect on the isolated guinea pig trachea in vitro. This effect was indirectly dependent on the production and release of nitric oxide from nitrergic neurons and was directly dependent on the modulation of calcium-modulated potassium channels and high (BKCa) and intermediate (IKCa) conductances (Paulino et al., 2002)

Biological Activities

PLANTA MEDICA
An International Journal of Natural Products and Medicinal Plant Research
Official Organ of the Society for Medicinal Plant Research (GA),
www.ga-online.org

PAULINO, N. ; TEIXEIRA, C. ; MARTINS, R. ; SCREMIN, A. ; DIRSCH, V. ; VOLLMAR, A. ; ABREU, S. R. L. ; CASTRO, S. L. ; MARCUCCI, M. C. . Evaluation of the analgesic and anti-inflammatory effects of a Brazilian green propolis.. Planta Medica, v. 72, p. 899-906, 2006

We published an article on the analgesic and anti-inflammatory activity of the propolis of Baccharis dracunculifolia from Brazil. We demonstrated that Baccharis dracunculifolia's propolis produced an anti-edema, anti-inflammatory and analgesic effect when evaluated using various animal models and in molecular biology methods. Baccharis dracunculifolia propolis inhibited the production of prostaglandin E2 during the acute inflammation phase, reduced the production of nitric oxide in macrophages and inhibited the activation of the nuclear transcription factor (NF□B).

Biological Activities

Available online at www.sciencedirect.com
ScienceDirect
Veterinary Immunology and Immunopathology 116 (2007) 79–84
Veterinary immunology and immunopathology
www.elsevier.com/locate/vetimm

Adjuvant effect of green propolis on humoral immune response of bovines immunized with bovine herpesvirus type 5

Geferson Fischer [a,b,*], Marlete Brum Cleff [b], Luana Alves Dummer [a,b], Niraldo Paulino [c], Amarílis Scremin Paulino [c], Camila de Oliveira Vilela [b], Fabrício Souza Campos [b], Tiago Storch [b], Gilberto D'Avila Vargas [b], Silvia de Oliveira Hübner [b], Telmo Vidor [b]

[a] *Centro de Biotecnologia, Universidade Federal de Pelotas (UFPel), Campus Universitário, Caixa Postal 354, 96010-900, Pelotas, RS, Brazil*
[b] *Laboratório de Virologia e Imunologia, Faculdade de Veterinária, UFPel, Campus Universitário, Caixa Postal 354, 96010-900, Pelotas, RS, Brazil*
[c] *Faculdade de Farmácia, Departamento de Pesquisa e Extensão, Universidade Bandeirante de São Paulo, São Paulo, Brazil*

Received 19 October 2006; received in revised form 19 December 2006; accepted 9 January 2007

Demonstration of the immunomodulatory effect of typified green propolis on the humoral and cellular immune response. Propolis as a veterinary vaccine adjuvant.

Biological Activities

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect

Vaccine 25 (2007) 1250–1256

Vaccine

www.elsevier.com/locate/vaccine

Immunomodulation produced by a green propolis extract on humoral and cellular responses of mice immunized with SuHV-1

Geferson Fischer[a,b,*], Fabricio Rochedo Conceição[a,b], Fábio Pereira Leivas Leite[a,c], Luana Alves Dummer[a,b], Gilberto D'Avila Vargas[b], Sílvia de Oliveira Hübner[b], Odir Antônio Dellagostin[a,c], Niraldo Paulino[d], Amarílis Scremin Paulino[d], Telmo Vidor[b]

[a] *Centro de Biotecnologia, Universidade Federal de Pelotas (UFPel), CP 354, 96010-900 Pelotas, RS, Brazil*
[b] *Laboratório de Virologia e Imunologia, Faculdade de Veterinária, UFPel, CP 354, 96010-900 Pelotas, RS, Brazil*
[c] *Instituto de Biologia, UFPel, CP 354, 96010-900 Pelotas, RS, Brazil*
[d] *Curso de Farmácia, Universidade Barriga Verde, UNIBAVE, Rua Miguel Couto 330, 88870-000 Orleans, SC, Brazil*

Received 4 September 2006; received in revised form 4 October 2006; accepted 4 October 2006
Available online 18 October 2006

Demonstration of the immunomodulatory effect of typified green propolis on the humoral and cellular immune response. Propolis as a veterinary vaccine adjuvant.

Biological Activities

INTERNATIONAL JOURNAL OF CANCER RESEARCH

International Journal of Cancer Research 3 (1): 43-53, 2007
ISSN 1811-9727

Biological Therapy Using Propolis as Nutritional Supplement in Cancer Treatment

J. Galvao, J.A. Abreu, T. Cruz, G.A.S. Machado, **P. Niraldo**, A. Daugsch, C.S. Moraes, P. Fort and Y.K. Park F. Biological Therapy Using Propolis as Nutritional Supplement in Cancer Treatment. International Journal of Cancer Research 3 (1): 43-53, 2007

Review of the indication for the use of propolis as an adjunctive nutritional therapy in the treatment of cancer, which refers to this effect based on numerous studies published in the literature.

Biological Activities

European Journal of Pharmacology 587 (2008) 296–301

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Anti-inflammatory effects of a bioavailable compound, Artepillin C, in Brazilian propolis

Niraldo Paulino [a,b,*], Sheila Rago Lemos Abreu [a,b], Yoshihiro Uto [c], Daisuke Koyama [c], Hideko Nagasawa [c], Hitoshi Hori [c], Verena M. Dirsch [d], Angelika M. Vollmar [d], Amarilis Scremin [e], Walter A. Bretz [f]

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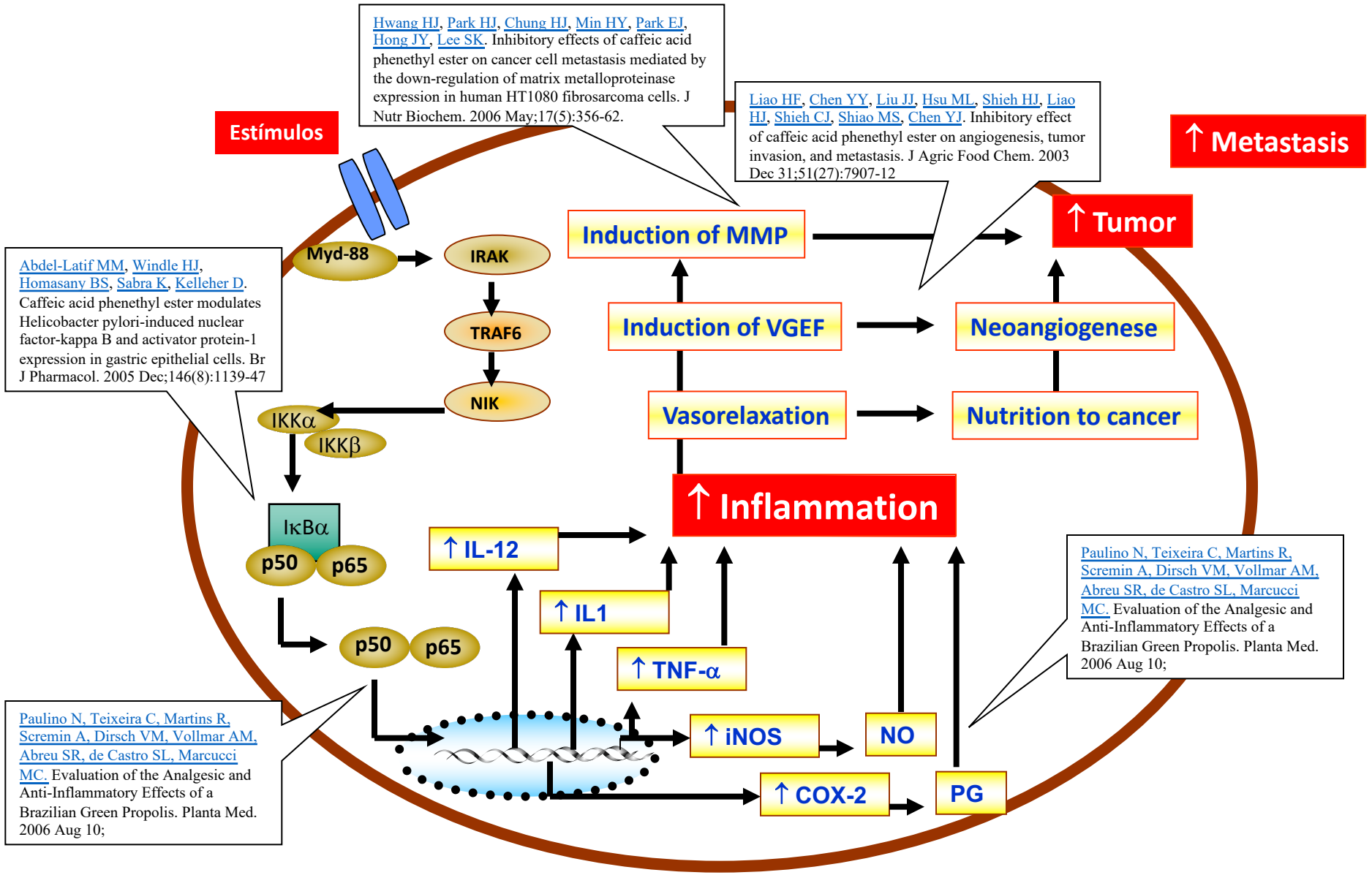
[b] Pharmacy Department, Centro Universitário Barriga Verde, Orleans, Brazil
[c] Department of Life System, Institute of Technology and Science, The University of Tokushima Graduate School, Minamijosanjimacho-2, Tokushima, Japan
[d] Dpartment of Pharmacy, University of Munich, Munich, Germany
[e] Departament of Pharmancy, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil
[f] New York University, College of Dentistry, New York, NY, USA

Evaluation of the anti-inflammatory activity and bioavailability of the compound Artepillin C present in the typified green propolis.

Pharmacological Mechanisms

Anti-inflammatory action of propolis and / or its constituents

Reduction of inflammation and angiogenesis



Niraldo Paulino[1]
Cristiane Teixeira[1]
Regiane Martins[1]
Amarilis Scremin[1]
Verena M. Dirsch[2]
Angelika M. Vollmar[2]
Sheila R. L. Abreu[3]
Solange L. de Castro[4]
Maria Cristina Marcucci[5]

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DOI 10.1055/s-2006-947185 · Published online 2006
ISSN 0032-0943

Evaluation of the Analgesic and Anti-Inflammatory Effects of a Brazilian Green Propolis

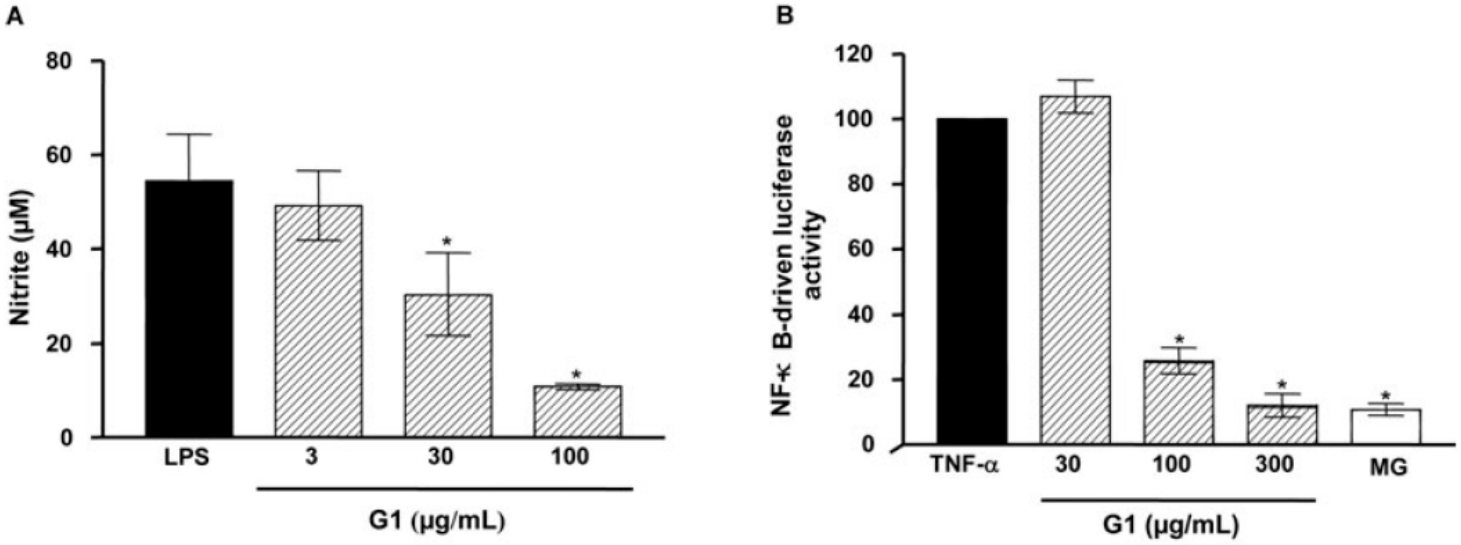
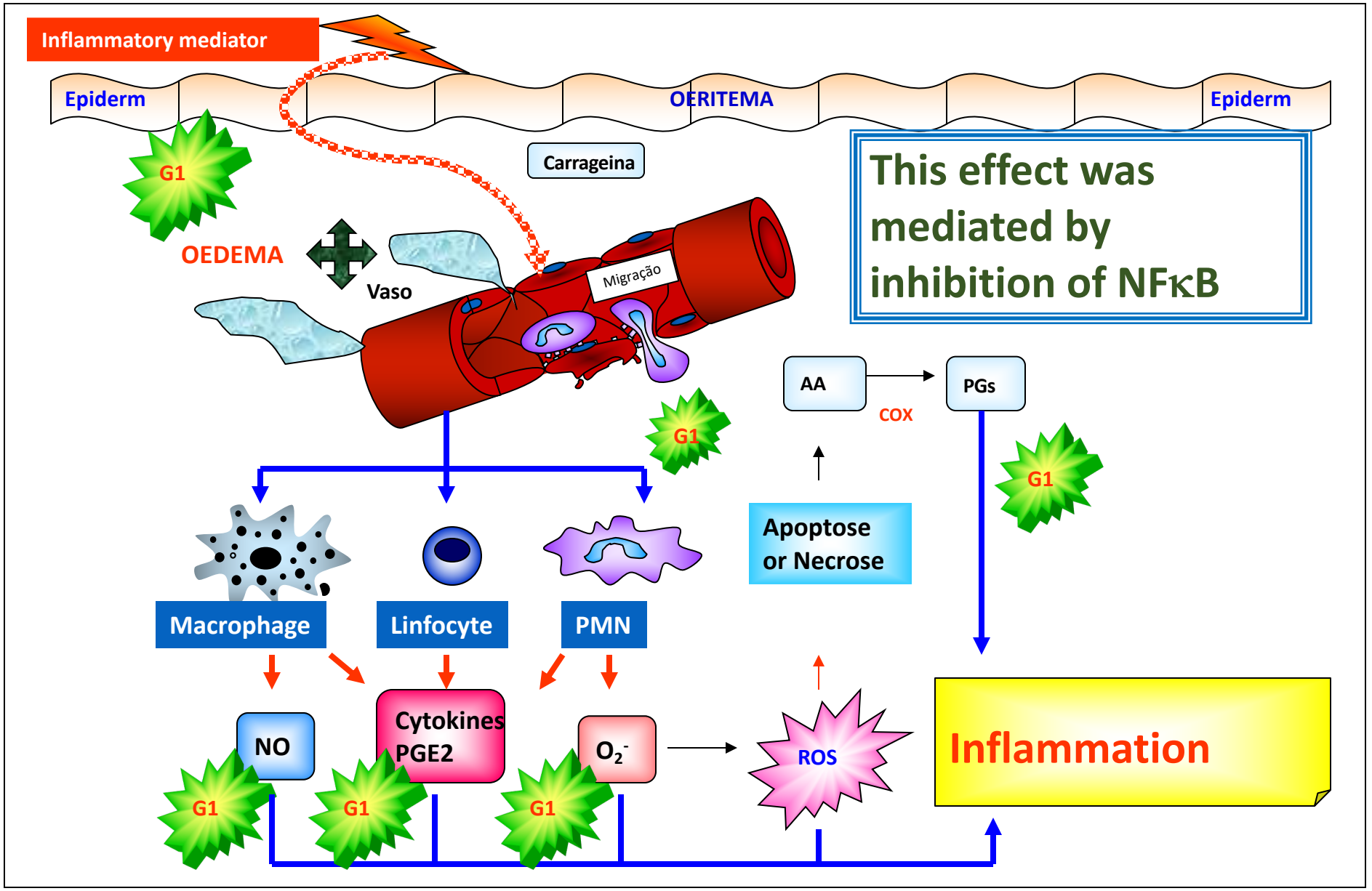


Fig. 6 Effect of treatment with **G1** of cell lineages: (**A**) nitrite production by RAW 264.7 cells stimulated with 1 µg/mL LPS for 20 h and treated with the extract (3 to 100 µg/mL); (**B**) luciferase activity in HEK 293 cell transiently transfected with a NF-κB-driven luciferase reporter gene by the extract (3 to 300 µg/mL) of 10 µM MG 132. Bars represents the mean ± S.E.M. of three independent experiments performed in triplicate, and asterisks indicate significant inhibition of the enzyme activity in relation to the untreated group, $P < 0.05$.

Conclusion: propolis is anti-inflammatory, reduces the production of nitric oxide and reduces the activity of NF-kappa B (NF :B: p50-p65).

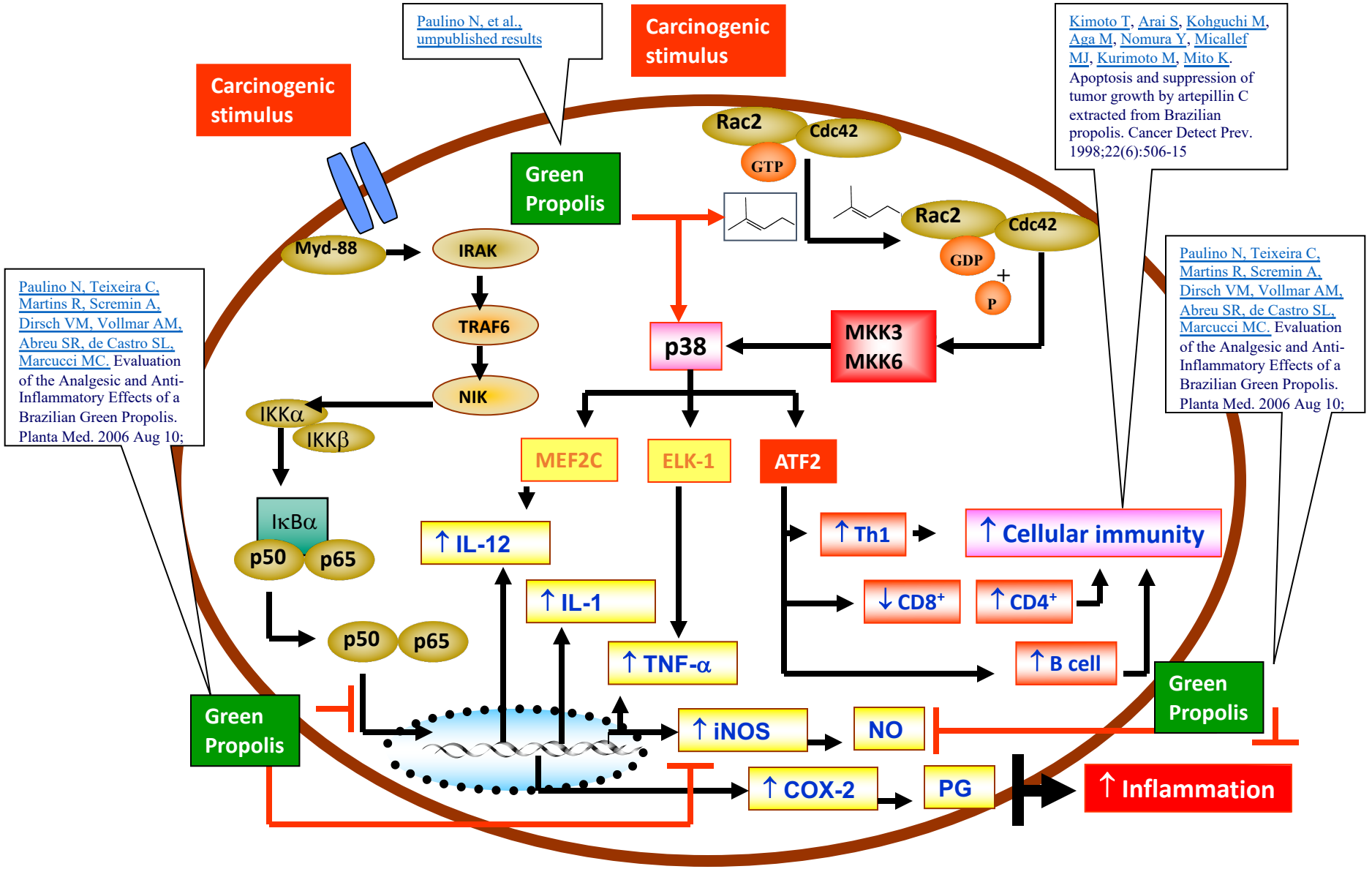
Paulino N, Teixeira C, Martins R, Scremin A, Dirsch VM, Vollmar AM, Abreu SR, de Castro SL, Marcucci MC. Evaluation of the Analgesic and Anti-Inflammatory Effects of a Brazilian Green Propolis. Planta Med. 2006 Aug 10.



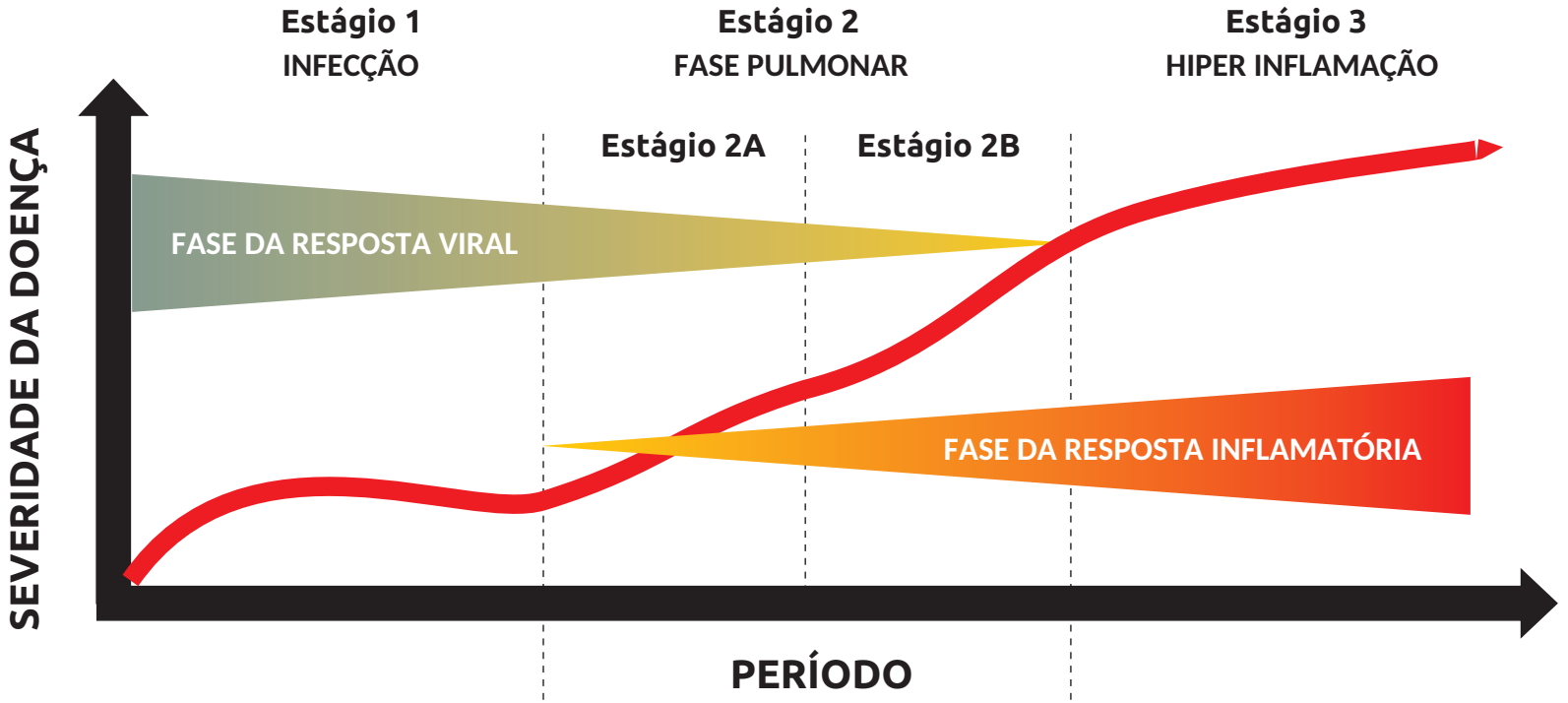
Pharmacological Mechanisms

Immunomodulatory action of propolis and / or its constituents

Regulation of the immune system and T lymphocytes



Pathophysiology of SARS-CoV-2 infection



SINTOMAS CLÍNICOS	Sintomas leves e não específicos, como mal-estar, diarréia, tosse seca. 37 graus de febre	Falta de ar Ausência de oxigênio / hipoxia 300mmHG	Síndrome do desconforto respiratório agudo (SDRA). Síndrome da resposta inflamatória sistêmica (SRIS/Choque). Insuficiência Cardíaca.
SINAIS CLÍNICOS	Nível baixo de linfócitos no sangue. Aumento do tempo de protrombina (TP) (aumento do tempo necessário para estancar uma hemorragia), Aumento do Dímero-D (pode indicar trombose) e exame LDH leve	Imagem torácica anormal. Transaminite (transaminases elevadas/função do fígado). Procalcitonina (PCT) baixa normal.	Marcadores de inflamação elevados (CRP, LDH, IL-6, D-dimer, ferritina). Troponina e NT-ProBNP elevados.
POSSÍVEIS TRATAMENTOS (obs.: em testes)	**REMDESIVIR, CLOROQUINA, HIDROXICLOROQUINA, TRANSFUSÃO DE PLASMA**		
	REDUZIR A IMUNOSSUPRESSÃO	**CORTICOIDE, IMUNOGLOBULINA HUMANA, INIBIDOR DE INTERLEUCINA 6 (IL-6)/TOCILIZUMABE, INIBIDOR IL-2, INIBIDORES DE JAK.**	

Open Access Full Text Article

COMMENTARY

Hypercytokinemia and Pathogen–Host Interaction in COVID-19

Hypercytokinemia in the interaction between the pathogen and the host in Covid-19

This article was published in the following Dove Press journal:
Journal of Inflammation Research

Alaa Badawi[1,2]

[1]Public Health Risk Sciences Division, Public Health Agency of Canada, Toronto, ON, Canada; [2]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, ON, Canada

Abstract: Severe acute respiratory syndrome (SARS) coronavirus (CoV)-2 (SARS-CoV-2) is a novel coronavirus identified as the cause of coronavirus disease-2019 (COVID-19) that began in Wuhan, China in late 2019 and spread now in 210 countries and territories around the world. Many people are asymptomatic or with mild symptoms. However, in some cases (usually the elderly and those with comorbidities) the disease may progress to pneumonia, acute respiratory distress syndrome and multi-organ dysfunction that can lead to death. Such wide interindividual differences in response to SARS-CoV-2 infection may relate to several pathogen- and host-related factors. These include the different levels of the ubiquitously present human angiotensin I converting enzyme 2 (ACE2) receptors gene expression and its variant alleles, the different binding affinities of ACE2 to the virus spike (S) protein given its L- and S-subtypes and the subsequent extent of innate immunity-related hypercytokinemia. The extensive synthesis of cytokines and chemokines in coronavirus diseases was suggested as a major factor in exacerbating lung damage and other fatal complications. The polymorphisms in genes coding for pro-inflammatory cytokines and chemokines have been associated with mediating the response and susceptibility to a wide range of infections and their severe outcomes. Understanding the nature of pathogen–host interaction in COVID-19 symptomatology together with the role of hypercytokinemia in disease severity may permit developing new avenues of approach for prevention and treatment and can delineate public health measures to control the spread of the disease.

Keywords: SARS-CoV, MERS-CoV, SARS-CoV-2, COVID-19, hypercytokinemia

SARS-CoV-2 triggers the gene expression of pro-inflammatory cytokines (Il1, Il12 TNFα) mediated by the activation of the nuclear transcription factor kappa B (NFκB)

That generate an inflammatory condition and promote an increase in oxidative stress, cell destruction and the participation of the affected organs.

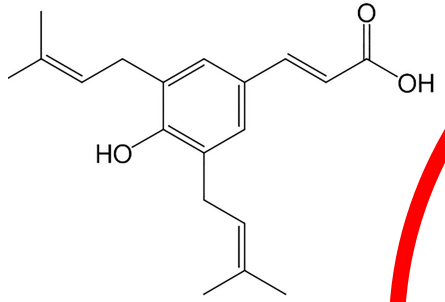
Journal of Inflammation Research 2020:13 255–261

Reduction of inflammation and angiogenesis

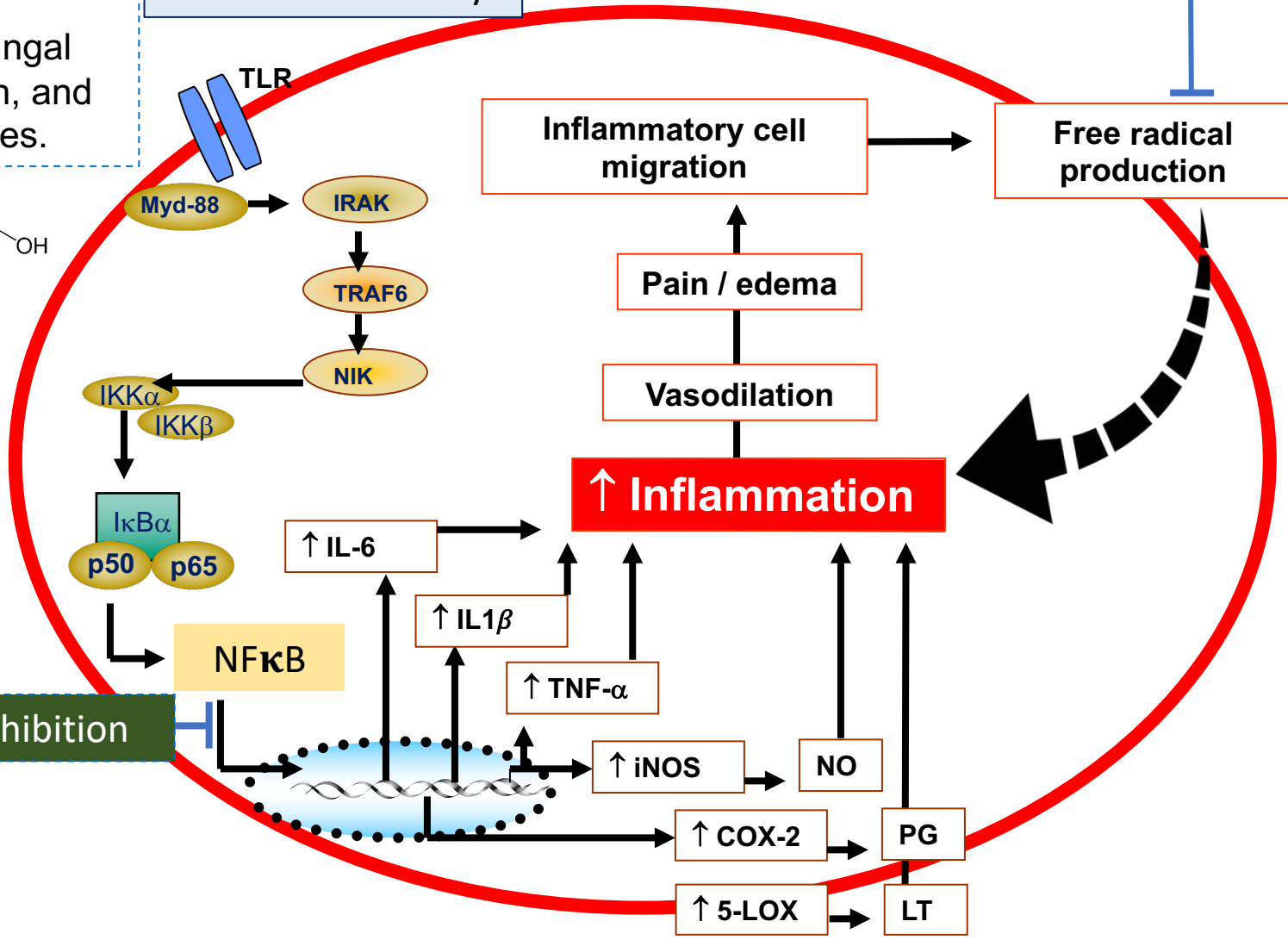
Cytopropolis — Antiviral — Antimicrobian — Antioxidant — Anti-inflammatory

Cytopropolis inhibits NFκB and scavenges free radicals.

Treatment of Viral, bacterial, and fungal infections, inflammation, and degenerative diseases.



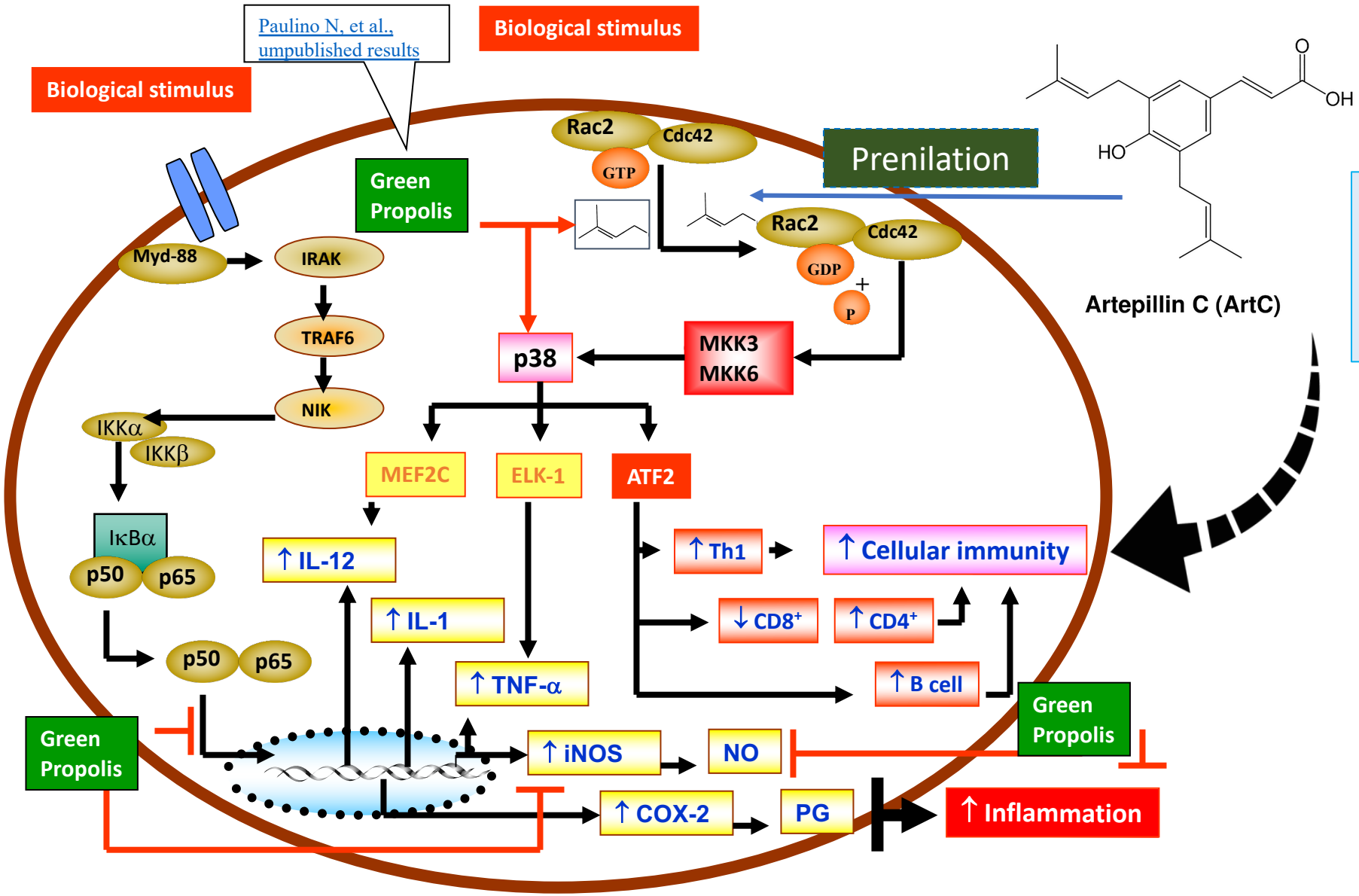
Artepillin C (ArtC)



Cytopropolis 700mg
Excipient qsp ..... 1 capsule
Dosage: must be used orally
na dose of 1 (amu) capsule, 3 (three) times a day.

www.fitoandhealth.com

Regulation of the immune system and T lymphocytes



Artepillin C (ArtC)

Cytopropolis increases the post-translational prenylation of RAS-GTPase proteins and stimulates the cellular immune response.

CLINICAL EVIDENCE

Are the preclinical effects reproducible in humans with cancer during nutritional supplementation with propolis?

Pharmacology

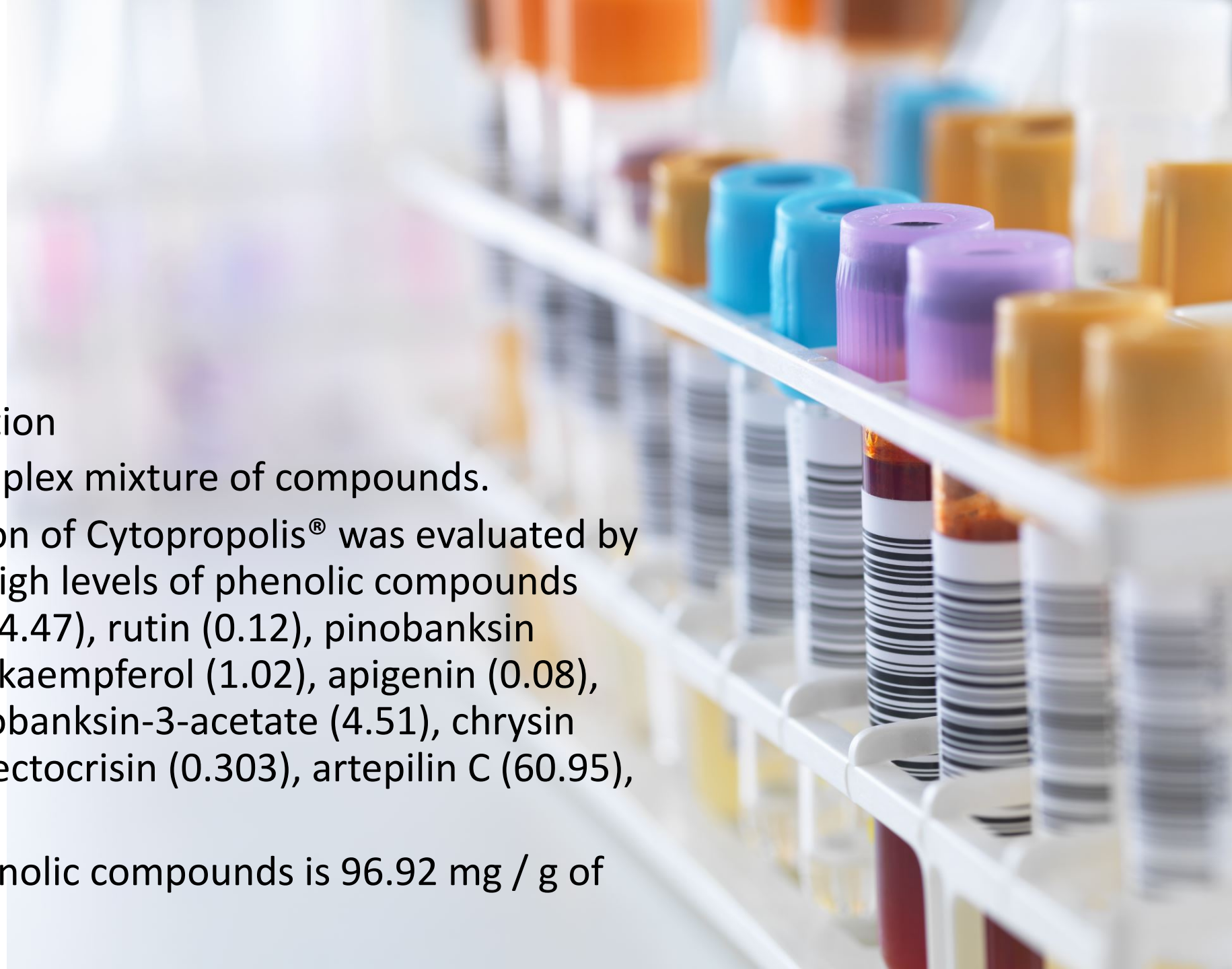
PHARMACOKINETICS

Absorption and distribution

Cytopropolis® has a complex mixture of compounds.

The chemical composition of Cytopropolis® was evaluated by HPLC analysis showing high levels of phenolic compounds (mg / g): coumaric acid (4.47), rutin (0.12), pinobanksin (5.38), quercetin (0.31), kaempferol (1.02), apigenin (0.08), pinocembrin (0.71), pinobanksin-3-acetate (4.51), chrysin (0.70), galangin (0.63), tectocrisin (0.303), artepilin C (60.95), Bacarin (17.76) .

The total content of phenolic compounds is 96.92 mg / g of dry extract.



Pharmacology

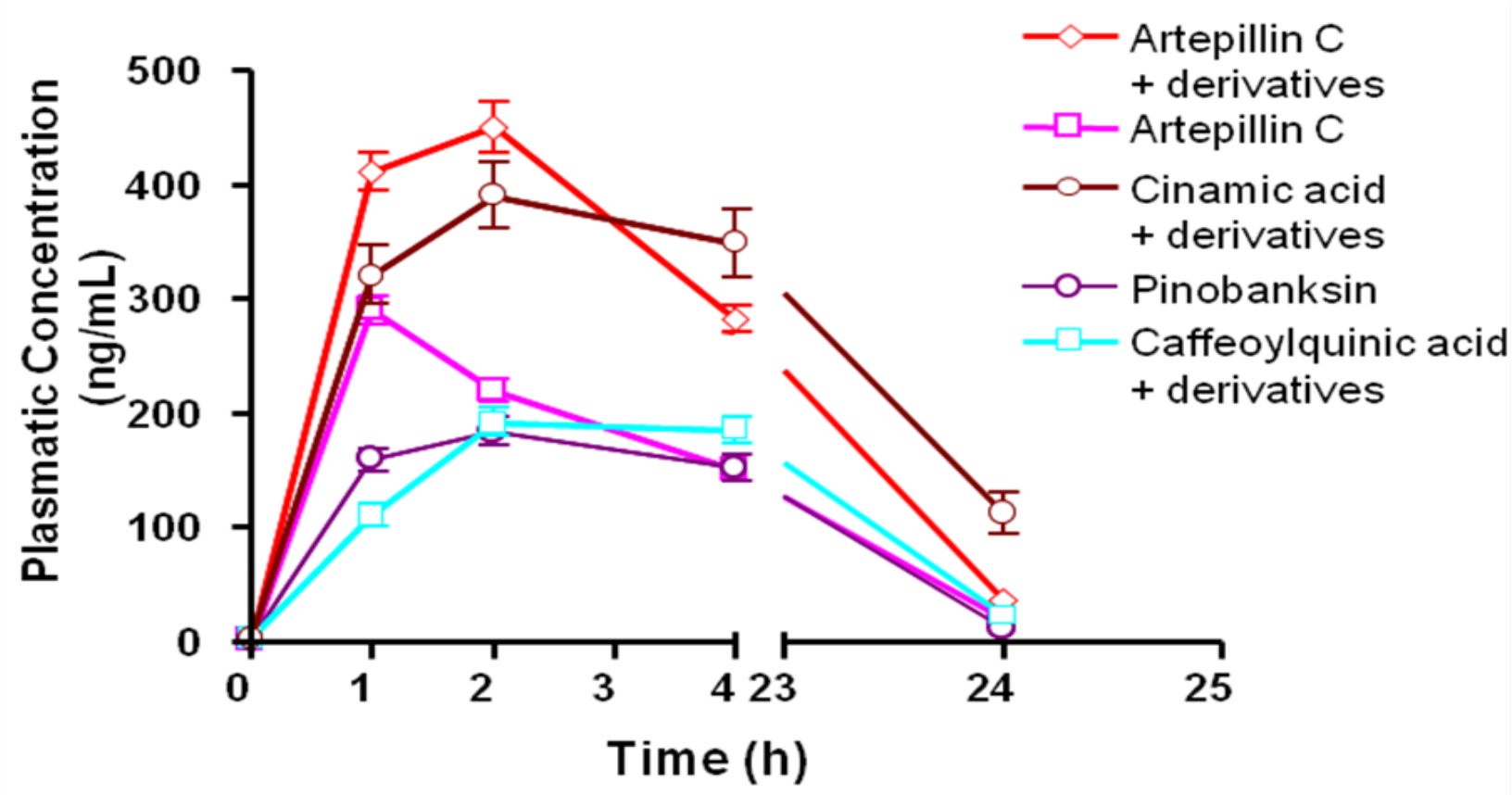
PHARMACOKINETICS

Absorption and distribution - Clinical pharmacokinetic study:

* 20 volunteers (18-25 years of both sexes);
* 6 Cytopropolis® capsules (700 mg each) / volunteer;
* Blood collected after 1, 2, 4 and 24 hours after consuming Cytopropolis®;
* Blood was treated and the plasma concentration of phenolic compounds was evaluated by an HPLC assay.
* Cytopropolis® Pharmanectar (batch PADE1105-BIO, manufactured in 2005/11)

Pharmacology

Absorption and distribution - Clinical pharmacokinetic study:



Evaluation of plasma concentrations of Artepilin C and related phenolic compounds in humans after consuming Cytopropolis®. Each point represents the mean ± SEM of the concentrations of phenolic compounds (ng / mL).

Biological Activities

Câmara Técnica de Medicamentos Fitoterápicos - CATEF

Federal Agricultural Legislation (MINISTRY OF AGRICULTURE, 2001) regulated the identity and quality for propolis, setting the minimum quality requirements for its commercialization

At the end of 2005, Anvisa published a technical note regulating the registration of medicines made from propolis, provided that they have therapeutic indications proven by scientific experiments.

(www.anvisa.gov.br/medicamentos/catef/propolis.htm).

There is a demand for the registration of products with therapeutic indication, containing propolis, as an asset, alone or in association.

Propolis is a natural product, with resinous physical characteristics and variable composition, collected from various plant species and which undergoes the addition of secretions from the bee, being classified as opotherapeutic. The requirements for your registration are defined in RDC No. 132/2003 and proof of safety and effectiveness is detailed in this technical note.

Cosmetics and cosmeceuticals

Nutritional supplementation

(pharmacokinetic assay)

The propolis samples were prepared by the company Farmacêutica Ltda (Lote PADE1105-BIO, fab. In 2007/11) with analysis reports for chemical and origin certification. The quality standards of the company Néctar Farmacêutica Ltda were certified by ISO 9001 / GMP and by five other institutional accreditation bodies: SIF and INMETRO (Brazil), DNV (Germany), JAB (Japan) and UKAS (United Kingdom). Artepillin C® was kindly provided by Prof. Dr. Hitoshi Hori and Yoshihiro Uto of the Department of Biological Science & Technology, Faculty of Engineering, The University of Tokushima, Tokushima, Japan.

Pharma Nectar

DNV JAB QS Accreditation R020 UKAS QUALITY MANAGEMENT

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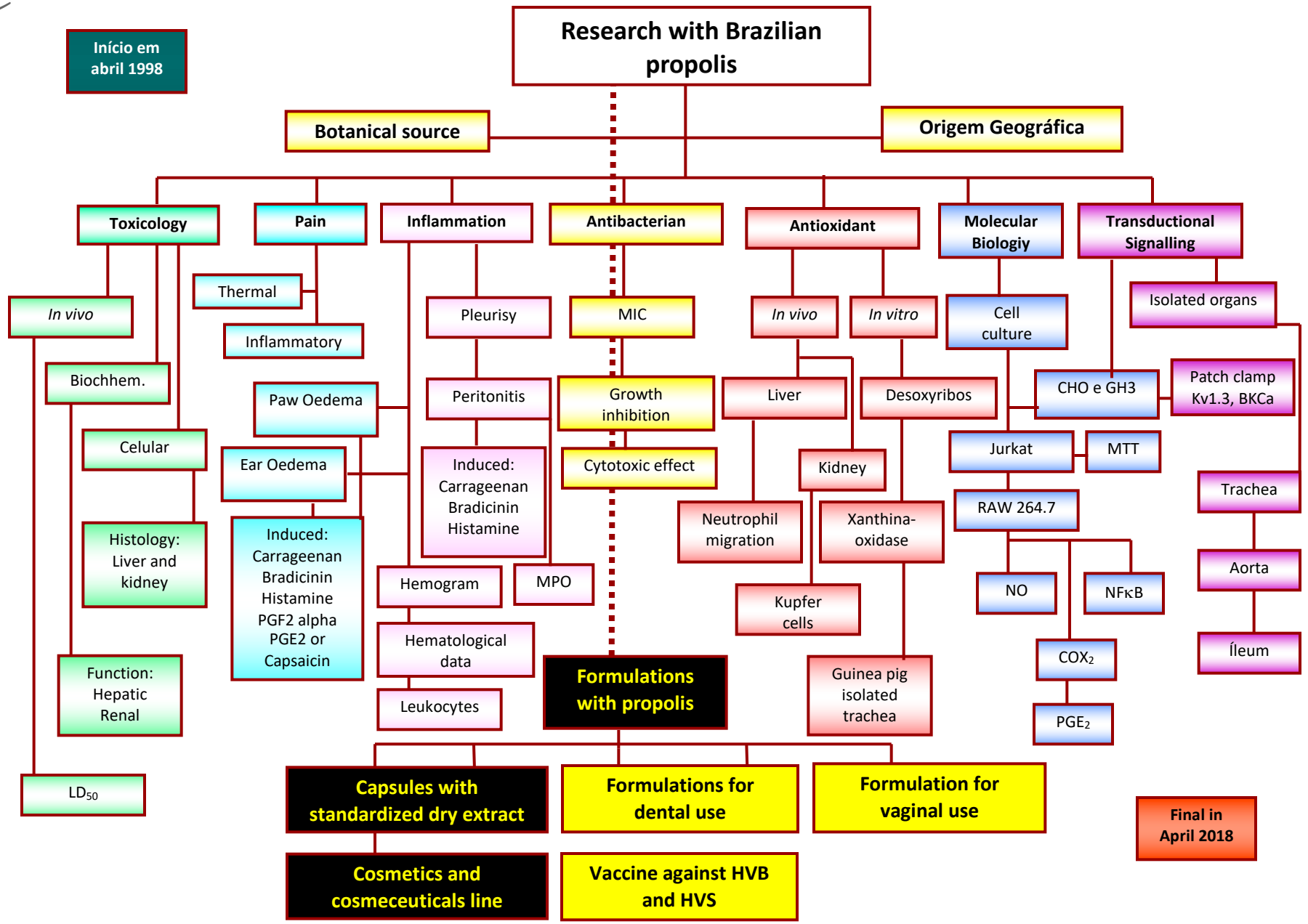
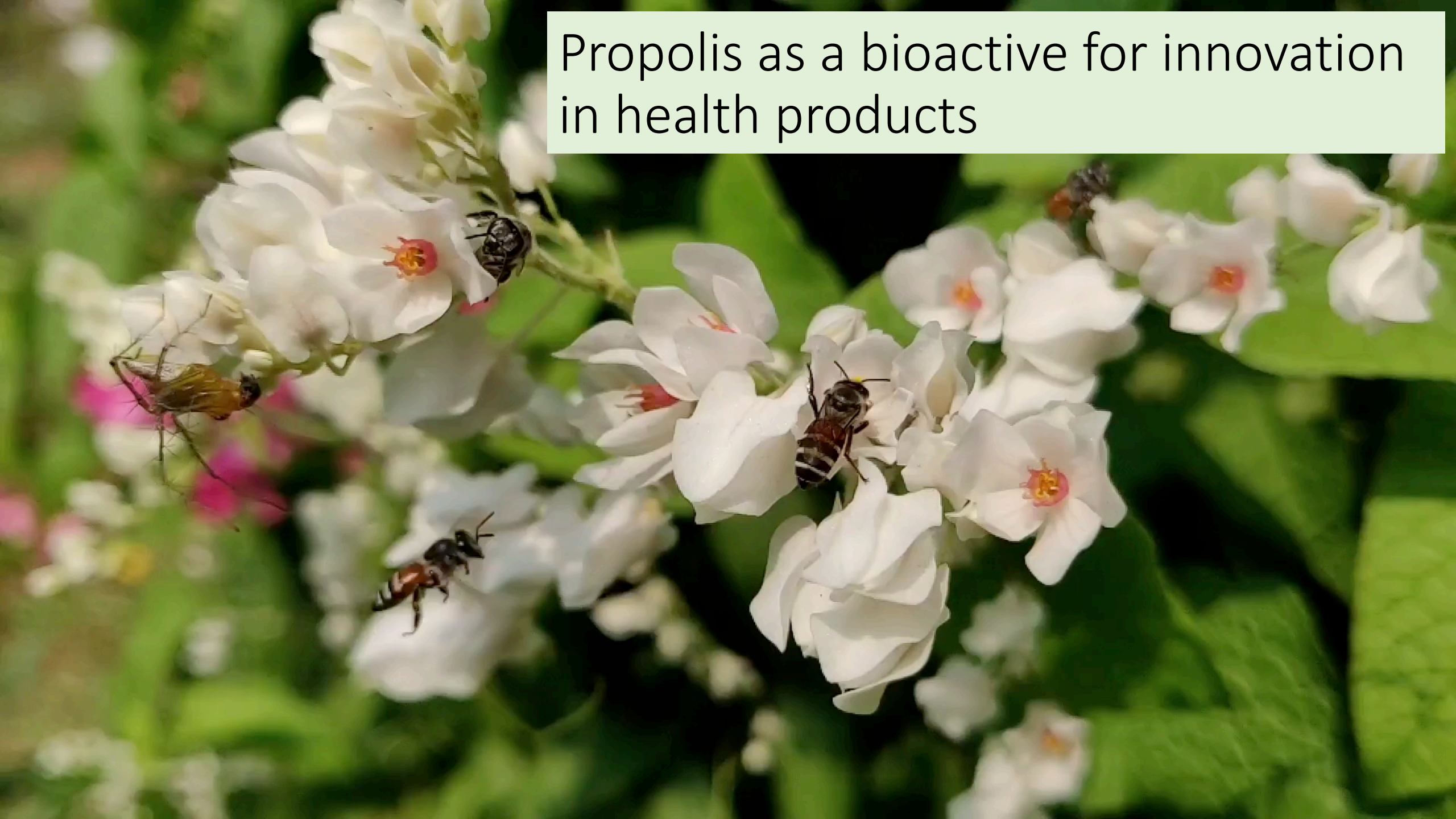
DNV AS, REGION JAPAN

Certified Quality System Marks

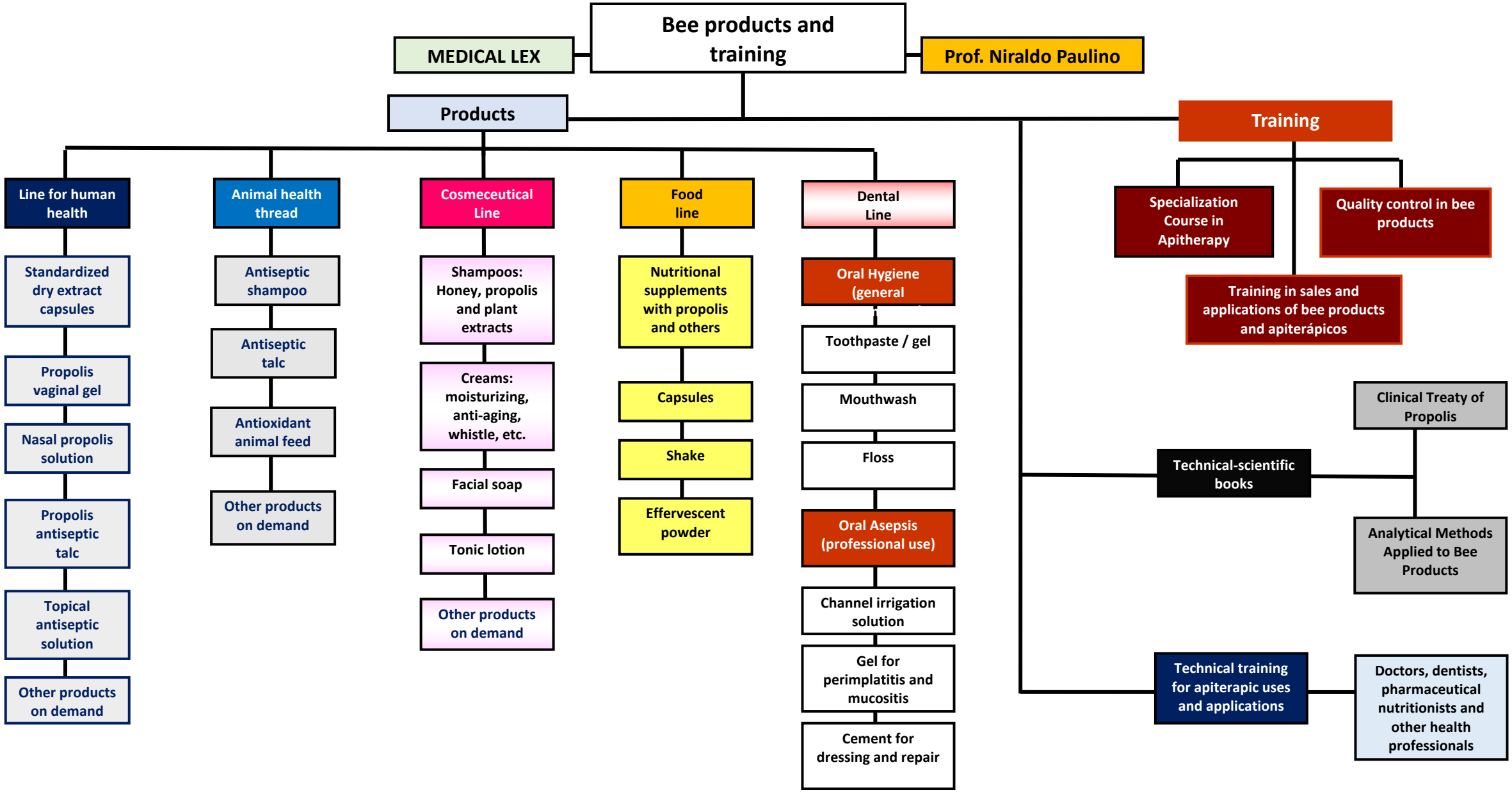
Brazilian Propolis Study



Propolis as a bioactive for innovation in health products



Challenges of innovation and diversification with propolis



Thank you

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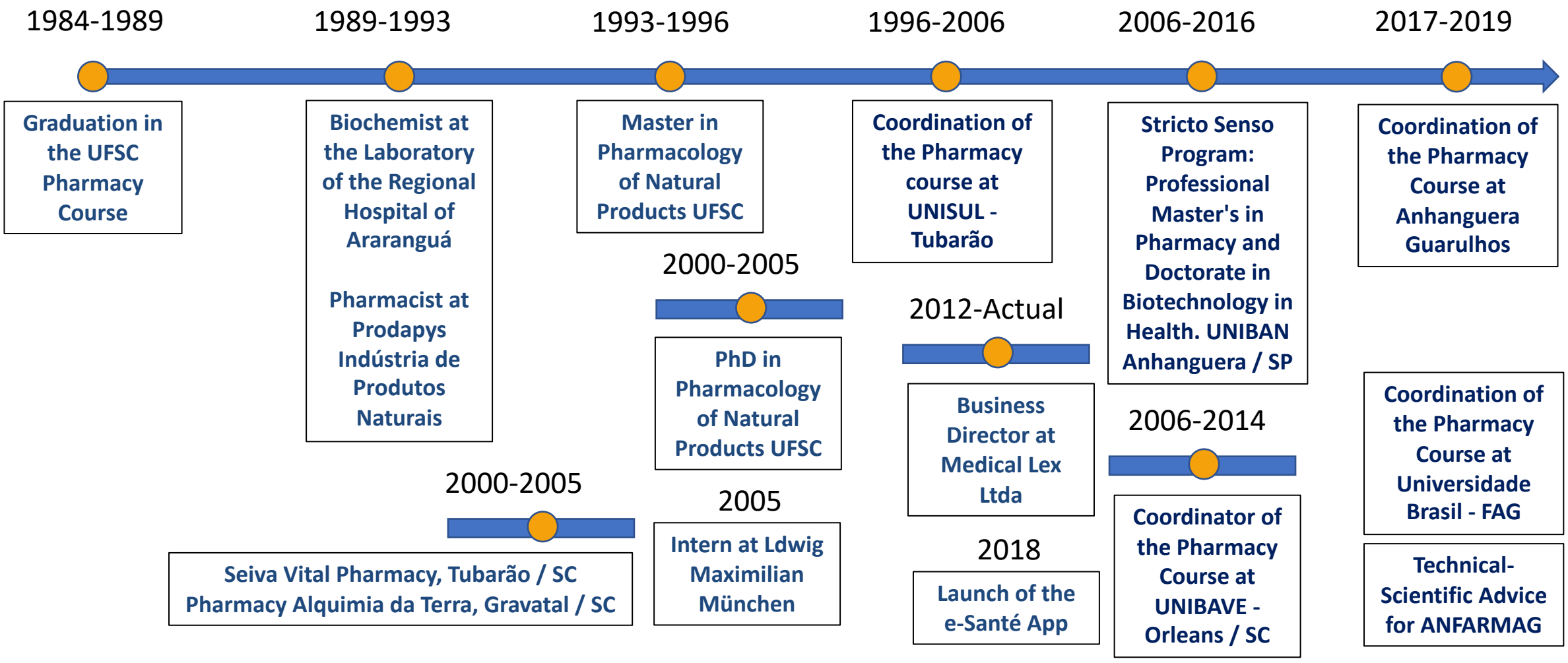
Prof. Dr. Niraldo Paulino

2020

Professional Chronology



Prof. Dr. Niraldo Paulino

Brands that helped consolidate

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Vet Immunol Immunopathol. 2007 Mar 15;116(1-2):79-84. Epub 2007 Jan 14

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