OP-044 [Apitherapy]
Propolis: Research, Apitherapy and Clinical Applications

Jose Mauricio Sforcin
São Paulo State University (UNESP), Institute of Biosciences, Campus Botucatu

Mankind has benefited from bee products for treating and preventing various illnesses. Apitherapy has been used in several countries as a complementary medicine. Scientific research based on studies carried out in vitro, using cell cultures, and in vivo, studying experimental animals, have demonstrated propolis biological properties, showing a strong relationship with apitherapy and providing support for clinical trials. In apitherapy, propolis has been used not only externally but also internally to treat a great variety of diseases due to its abundance of constituents. Propolis has been indicated for flu and cold symptoms, skin disorders (wounds, burns, and acne), psoriasis, otorhinolaryngologic, gynecologic, and proctologic diseases, preventing caries and treating gingivitis or stomatitis. Propolis has also been studied in diabetes, asthma, HIV, and others. Propolis is indicated simultaneously with other bee products to reduce chronic inflammation. Medicines containing propolis have a positive effect in treating infections caused by antibiotic-resistant pathogens. In general, propolis is safe and may be also consumed by healthy individuals or patients, without affecting the effect of medications. The standardization of propolis and its use in apitherapy are still under discussion, as apitherapy is practiced in some parts of the world, bringing benefits for healthy individuals and patients, with no clear consensus on its application according to the world regions or prevalent use of propolis and treated diseases. There are different recommendations for the use of propolis and people ingest different amounts of propolis once or several times a day. Although we have advanced in the knowledge of propolis properties, it is imperative to standardize its use, communicating the results at scientific and alternative events to strengthen the exchange of information between beekeepers, researchers, apitherapists, nutritionists, physicians, sellers and consumers of propolis. Otherwise, we will be always working separately, without complementing our expertise.

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Instituto de Biociências de Botucatu - Unesp

49th Apimondia Congress

"Propolis:

Research, Apitherapy and Clinical Applications"

Prof. José Maurício Sforcin
Full Professor in Immunology
Institute of Biosciences – São Paulo State University (UNESP)
18618-691 – Botucatu, SP – Brazil

RESEARCH:

in vitro or *in vivo*???

Which model(s)?

What kind of propolis extract?

Which concentrations?

etc...

IN VITRO

studies using cell cultures revealed an abundance of properties:

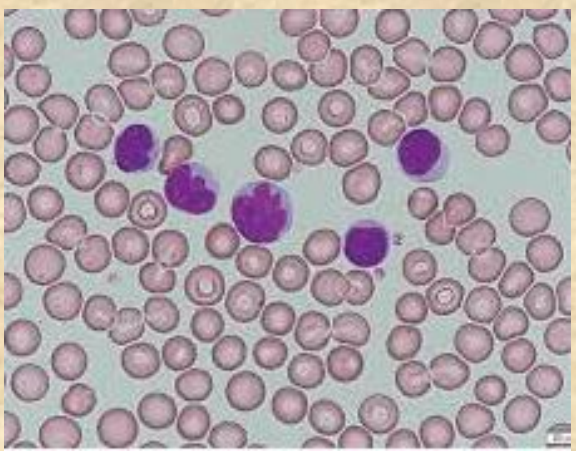
anti-inflammatory / immunomodulatory

antimicrobial (bacteria, virus, yeasts)

cytotoxic action against tumor cells

antioxidant

lately: COVID-19



IN VIVO

studies with experimental animals:

anti-inflammatory / immunomodulatory
wound and burn healing
antihypertensive
analgesic
hepatoprotective
antidiabetic and hypolipidemic

antitumor
anti-allergic
antidepressant and anxiolytic
neuroprotective
antioxidant

asthma
chronic gastric ulcer
colitis
ovary injury
cerebral injury

(Weis et al., 2022)

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Review

Propolis: Is there a potential for the development of new drugs?

José Maurício Sforcin[a,*], Vassya Bankova[b]

[a] Department of Microbiology and Immunology, Biosciences Institute, UNESP, 18618-000 Botucatu, SP, Brazil
[b] Institute of Organic Chemistry with Centre of Phytochemistry, Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

CANDIDATE AREAS:

Immunity
Tumor
Infections
Ulcer
Allergy, rhinitis and asthma
Diabetes

Propolis and the immune system: a review

J.M. Sforcin *

Table 1
Propolis immunomodulatory action according to its dose, chemical composition and main components, and assay conditions of some authors

Immunological assay	Reported outcome	Dose and route	*In vivo*/*in vitro*	Main groups or active components	Characterization	Authors
Antibody production	↑	500 μg/mouse (i.p.)	*In vivo*	NM	NM	Scheller et al. (1988)
Classical and alternative pathways of the complement system	↓	WSD (63–1000 μg/ml)	*In vitro*	Phenolic acids and their esters, phenolic alcohols, aldehydes and ketones, flavonoids, stilbenes, coumarins	HPLC, GC–MS	Ivanovska et al. (1995a)
Macrophages spreading and motility	↑	10^{-5} M	*In vitro*	5-Caffeoylquinic acid, chlorogenic acid, 4-caffeoylquinic acid, 4,5-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 3,4-dicaffeoylquinic acid	HPLC	Tatefuji et al. (1996)
Macrophages activation	↑ H_2O_2, ↓ NO	2.5–100 μg/ml	*In vitro*	Prenylated p-coumaric acid and benzopyranes, essential oils, aromatic acids, di- and triterpenes	GC, GC–MS, TLC	Orsi et al. (2000)
Lymphocyte proliferation	↓	5–100 μg/ml	*In vitro*	Prenylated p-coumaric acid and benzopyranes, essential oils	GC, GC–MS, TLC	Sá-Nunes et al. (2003)
	↓	2.5, 5 and 10 mg/kg (p.o.)	*In vivo*	Aromatic acids, di- and triterpenes		
Antibody production	↑	5, 10 and 20 mg/kg (p.o.)	*In vivo*	CAPE	NM	Park et al. (2004)
Antibody and IFN-γ production	↑	5 mg/dose (s.c.)	*In vivo*	Phenolic compounds, cinnamic acid, flavonoids (pinobanksin, kaempferol)	HPLC	Fischer et al. (2007)

NM, not mentioned; ↑, stimulant action; ↓, inhibitory action; i.p., intraperitoneal route; p.o., per oral; s.c., subcutaneous route; WSD, water-soluble derivate of propolis; GC, gas chromatography; GC–MS, gas chromatography–mass spectrometry; TLC, thin layer chromatography; HPLC, high performance liquid chromatography.

***in vivo* and *in vitro* assays**

different concentrations of propolis

different types of extract

intake period

routes of administration

(Sforcin, 2007)

Propolis antitumoral activity

Table 2
Propolis antitumor action according to its dose, effects, chemical composition and main components, and assay conditions of some authors

Tumor cell	Reported outcome	Dose and route	*In vivo*/*in vitro*	Main groups or active components	Characterization	Authors
HL-60 (human leukemia)	Apoptosis-like DNA fragmentation	1–200 μg/ml	*In vitro*	Artepillin C (3,5-diprenyl-4-hydroxycinammic acid)	HPLC	Matsuno et al. (1997b)
HLC (lung cancer), HCG (gastric cancer), Hepatoma, Melanoma	Suppression of tumor growth; ↑ ratio of CD4/CD8 T cells	500 μg (i.t.)	*In vivo*	Artepillin C	NM	Kimoto et al. (1998)
Yac-1 cells (murine lymphoma)	↑ Natural killer activity	10% (p.o.)	*In vivo*	Prenylated p-coumaric acid and benzopyranes, essential oils, aromatic acids, di- and triterpenes	GC, GC–MS, TLC	Sforcin et al. (2002a)
Colon carcinogenesis	↓ Aberrant crypt foci	10, 30 and 90 mg/kg (p.o.)	*In vivo*	Prenylated p-coumaric acid and benzopyranes, essential oils, aromatic acids, di- and triterpenes	GC, GC–MS, TLC	Bazo et al. (2002)
C6 glioma cells	↓ Viability, ↑ apoptosis	(10–400 μM)	*In vitro*	CAPE	NM	Lee et al. (2003)
MCa (transplantable mammary carcinoma)	↓ Tumor nodules, ↑ apoptosis or necrosis	WSDP (50 and 150 mg/kg) caffeic acid and CAPE (50 mg/kg) quercetin (1200 mg/kg) (p.o.)	*In vivo*	NM	NM	Orsolic et al. (2004)
Canine transmissible venereal tumor	↑ Cytotoxicity	10–100 μg/100 μl	*In vitro*	Prenylated p-coumaric acid and benzopyranes, essential oils, aromatic acids, di- and triterpenes	GC, GC–MS, TLC	Bassani-Silva et al. (in press)

NM, not mentioned; ↑, stimulant action; ↓, inhibitory action; p.o., per oral; WSDP, water-soluble derivate of propolis; i.t., intratumorally; GC, gas chromatography; GC–MS, gas chromatography–mass spectrometry; TLC, thin layer chromatography; HPLC, high performance liquid chromatography.

(Sforcin, 2007)

Inhibition of tumor cells

in vitro

Inhibition of tumor growth

in vivo

PROPOLIS ANTIMICROBIAL ACTION

in vitro **action against bacteria, virus, yeast, protozoa**

synergism with antibiotics

in vivo**??**

PROPOLIS ANTI-ULCER ACTIVITY

in vivo

Effect of Brazilian green propolis on experimental gastric ulcers in rats

Muriel Primon de Barros [a], João Paulo Barreto Sousa [b], Jairo Kenupp Bastos [b], Sérgio Faloni de Andrade [a,*]

Treatment (p.o.)	Dose (mg/kg)	Total area of lesion (mm^2)	% of lesion area	Ulcer Index	Inhibition (%)
Control	–	223.24 ± 26.12	31.24 ± 4.06	48.45 ± 5.87	–
Omeprazole	30	0.81 ± 0.81*	0.11 ± 0.11*	0.80 ± 0.80*	98.34
Green propolis extract	50	34.97 ± 8.10*	6.24 ± 1.32*	28.60 ± 4.63*	40.90
	250	37.79 ± 14.54*	4.39 ± 1.49*	27.00 ± 6.22*	44.21
	500	3.72 ± 2.47*	0.58 ± 0.36*	5.62 ± 3.29*	88.42

Journal of Ethnopharmacology 110 (2007) 567–571

CLINICAL TRIALS

Propolis: preventive or therapeutic intervention

DENTISTRY
(oral hygiene, toothpaste, mouthwash, root canal, hypersensitivity)

DIABETES

ASTHMA

INFECTIONS

COLON CANCER

WOUND HEALING

CANDIDIASIS

(Sforcin, 2016; Weis et al., 2022)

Table 3
Clinical trials with propolis: main approaches, types of trial, subjects and groups, types of intervention and main outcomes.

Approaches	Trial	Number of subjects/ groups	Propolis intervention	Main outcomes	Authors
Type 2 diabetes mellitus	Randomized double-blind placebo controlled	Placebo ($n = 30$) Propolis ($n = 30$)	Capsules 1500 mg/day 8 weeks	↓ fasting blood sugar ↓ 2-hp, insulin, HOMA-IR and HbA1c ↑ antioxidant capacity ↑ GPx and SOD	Afsharpour et al. (2019)
COVID-19 (Hospitalized patients)	Randomized controlled open-label single-center	Propolis 400 mg + standard care ($n = 40$) Propolis 800 mg/day + standard care ($n = 42$) control (standard care alone – $n = 42$)	Capsules 400 mg/day or 800 mg/day 7 days (followed for 28 days after admission)	Both doses: ↓ length of hospital stay 800 mg: ↓ acute kidney injury	Silveira et al. (2021)
HIV-infected people under antiretroviral therapy	Randomized double blind parallel-group placebo-controlled	Placebo ($n = 20$) Propolis ($n = 20$)	Tablets 500 mg/day 3 months	↑ Foxp3 expression ↑ CD4+ T cell proliferation ▪ Positive correlation: IL-10 and $CD4^+$ T cell count ▪ Negative correlation: IL-10 and IFN-γ	Conte et al. (2021)

(Weis et al., 2022)

Immunomodulatory/anti-inflammatory effects of a propolis-containing mouthwash on human monocytes

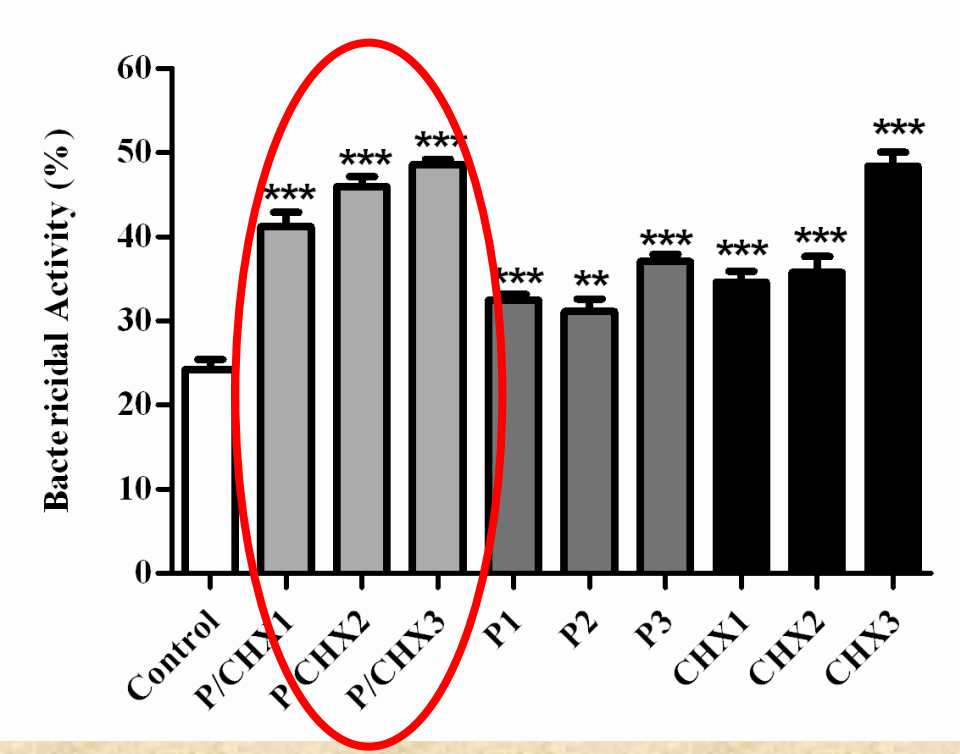
Karina Basso Santiago[1], Bruno José Conti[1], Eliza de Oliveira Cardoso[1], Marjorie de Assis Golim[2] and José Maurício Sforcin[1,*]

OXFORD FEMS JOURNALS investing in science

Pathogens and Disease, 74, 2016, ftw081

doi: 10.1093/femspd/ftw081
Advance Access Publication Date: 26 August 2016
Research Article

MOUTHWASH CONTAINING PROPOLIS



Percentage (%) of bactericidal activity of human monocytes incubated *in vitro* with propolis (P), chlorhexidine (CHX) and combination P/CHX and challenged with *Streptococcus mutans*.

$^{**}p < 0.001$; $^{***}p < 0.0001$ vs control (mean ± SD; n=10).

MOUTHWASH CONTAINING PROPOLIS
(Clinical trial – Patent)

(PIANA & SFORCIN, 2015)

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Biomedicine & Pharmacotherapy

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

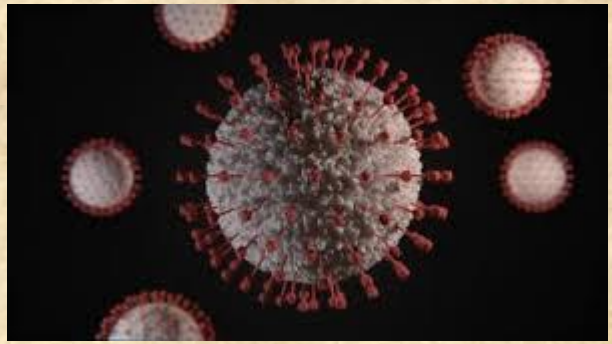
Original article

Efficacy of Brazilian green propolis (EPP-AF®) as an adjunct treatment for hospitalized COVID-19 patients: A randomized, controlled clinical trial

Patients hospitalized with COVID-19

standard care
standard care + propolis 400 mg/day
standard care + propolis 800 mg/day

The hospital stay post-intervention was shorter in both propolis groups compared to control



Journal of Ethnopharmacology 245 (2019) 112174

Contents lists available at ScienceDirect

Journal of Ethnopharmacology

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

Evaluation of potential herbal-drug interactions of a standardized propolis extract (EPP-AF®) using an *in vivo* cocktail approach

Interaction between a Brazilian propolis extract and commonly used drugs (caffeine, losartan, omeprazole, metoprolol, midazolam and fexofenadine)

Propolis did not alter the major CYP enzymes involved in drug metabolism, and was considered safe regarding potential interactions.

Phytomedicine Plus 2 (2022) 100239

Contents lists available at ScienceDirect

Phytomedicine Plus

journal homepage: www.sciencedirect.com/journal/phytomedicine-plus

An overview about apitherapy and its clinical applications

Wilson Antonio Weis [a], Nicolas Ripari [a], Fernanda Lopes Conte [a], Mariana da Silva Honorio [a], Arthur Alves Sartori [a], Ramon Hage Matucci [a], José Maurício Sforcin [a,*]

[a] São Paulo State University (UNESP), Institute of Biosciences, Department of Chemical and Biological Sciences, Campus Botucatu, 18618-691, Brazil

APITHERAPY

Propolis has been used externally and internally to treat:

flu and cold symptoms
skin disorders (wounds, acne)
to heal wounds and burns in post-traumatic and postoperative individuals
psoriasis
to prevent caries and to treat gingivitis

Propolis: indicated simultaneously with other bee products to reduce chronic inflammation

(Fokt et al., 2010; Fratellone, 2015; Habryka et al., 2016; Weis et al., 2022)

In general, propolis is safe,
well tolerated and nontoxic unless when administered in high amounts,
with rare adverse effects.

Propolis can be used by sick or healthy people.

Propolis: safer than many synthetic medicines,
but it is important to seek medical advice
before using it.

No consensus on propolis preparation,
doses, intake period and other conditions
to obtain the same effects
using propolis samples from different geographic regions.

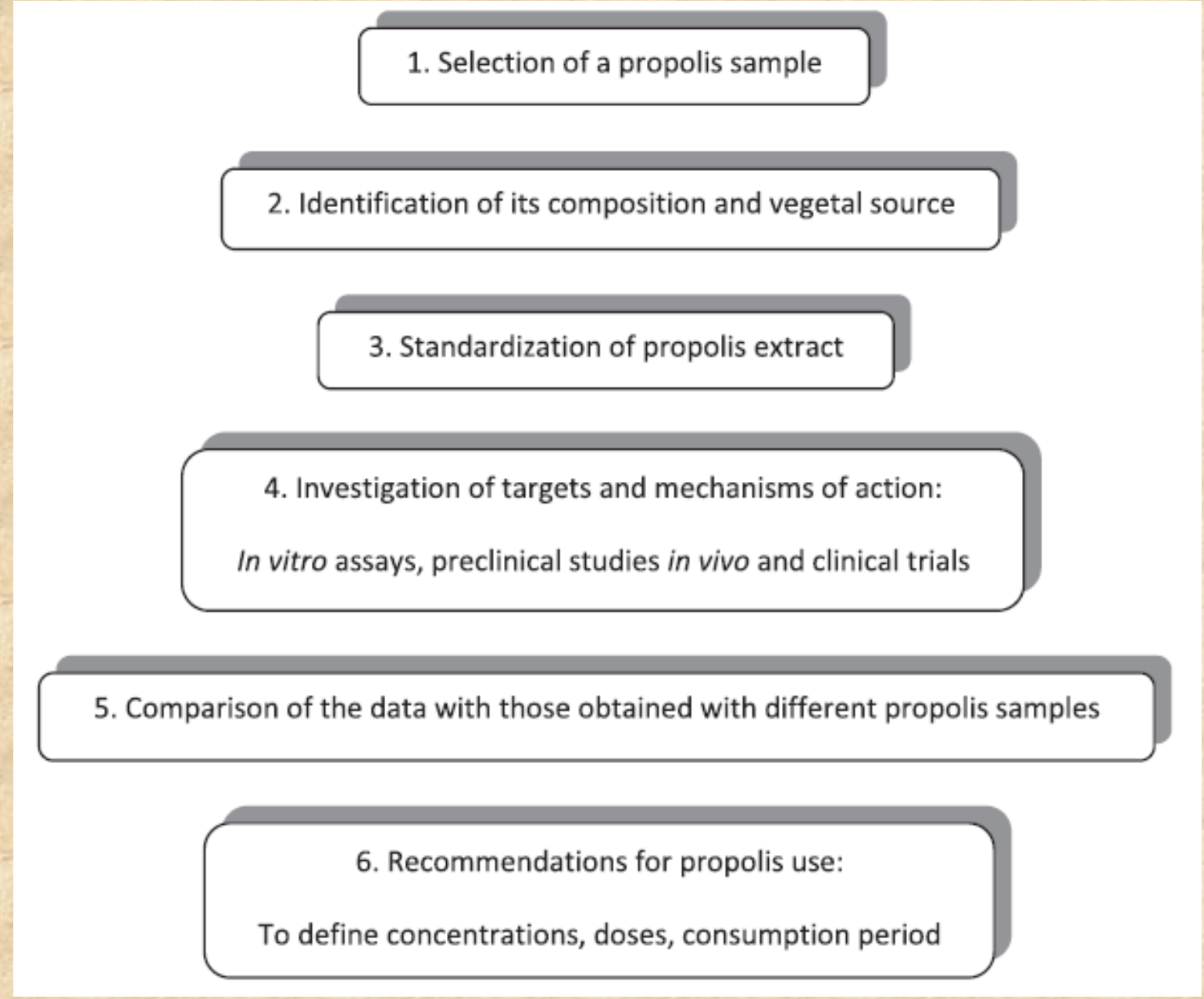
(Toreti et al., 2013; Braakhuis, 2019)

PHYTOTHERAPY RESEARCH
Phytother. Res. (2016)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.5605

REVIEW

Biological Properties and Therapeutic Applications of Propolis

José M. Sforcin*
Department of Microbiology and Immunology, Institute of Biosciences of Botucatu, UNESP, 18618-970, Botucatu, SP, Brazil



Steps to carry out a detailed investigation on a given propolis sample.

PROPOLIS

RESEARCH:

in vitro
in vivo
clinical trials

APITHERAPY

CLINICAL APPLICATIONS

↓

It is important to understand the conditions under which propolis may promote human health!

The importance of communicating the results in scientific and alternative events to reinforce the exchange of information between:

Beekeepers
Researchers
Apitherapists
Nutritionists
Physicians
Sellers
Consumers of bee products.

If not, we will always be working separately, without complementing our expertise.

ACKNOWLEDGEMENTS

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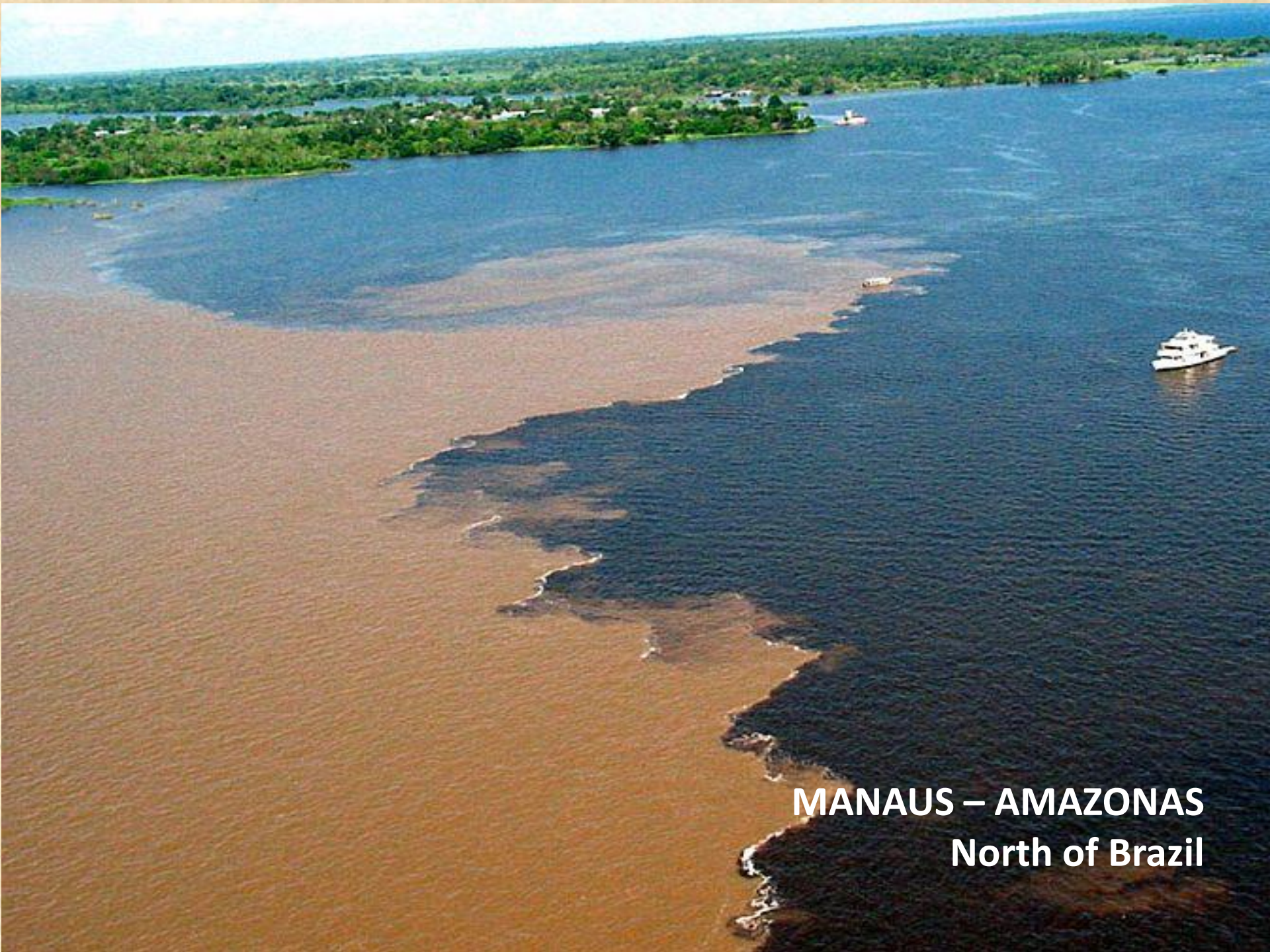
CAPES

E-mail: jose.m.sforcin@unesp.br

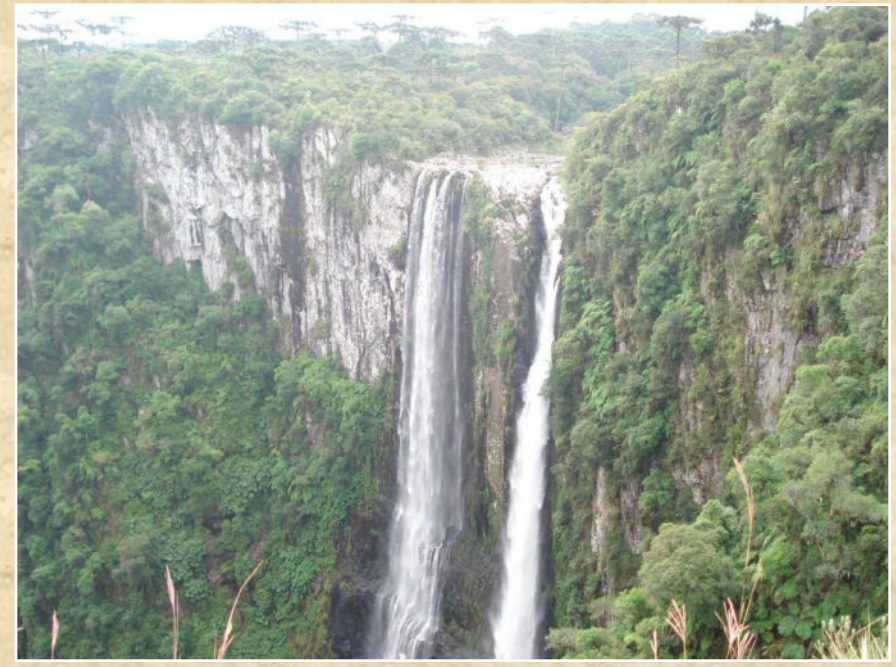
Laboratory of Immunomodulation by Natural Products (LIPNA)

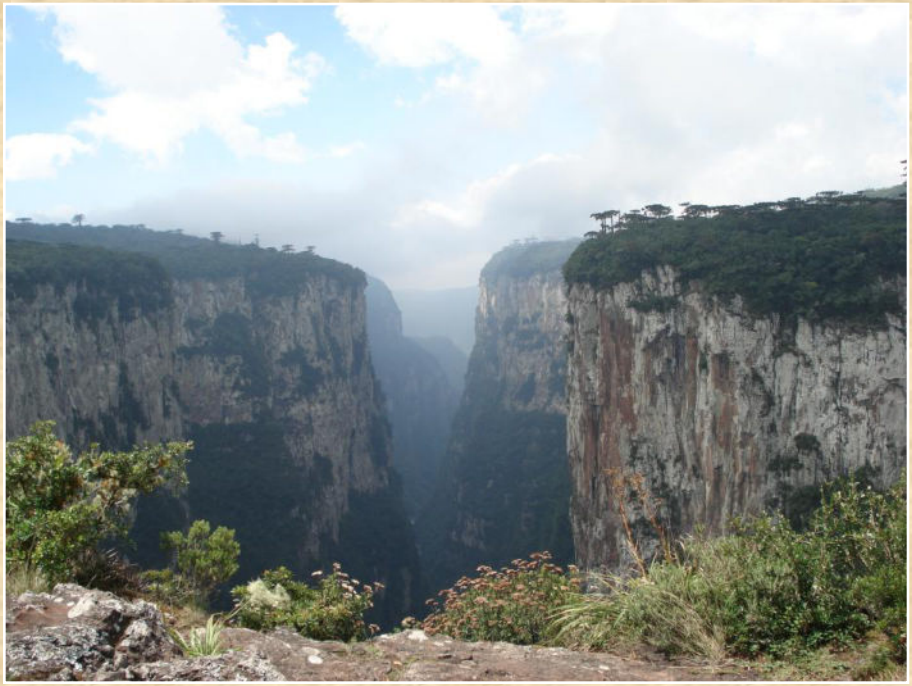
LIPNA
Laboratório de Imunomodulação por Produtos Naturais
Laboratory of Immunemodulation by Natural Products

INSTITUTE OF BIOSCIENCES – UNESP, BRAZIL


MANAUS – AMAZONAS
North of Brazil

BELÉM – PARÁ
North of Brazil





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FLORIANÓPOLIS
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