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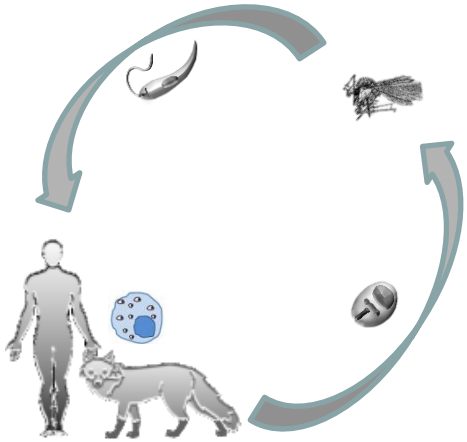
PHYTOTHERAPY: AN INNOVATIVE PERSPECTIVE IN LEISHMANIASIS TREATMENT

LUIZ FILIPE GONÇALVES DE OLIVEIRA

Fundação Oswaldo Cruz
Instituto Oswaldo Cruz
Laboratório de Biologia Molecular e Doenças Endêmicas

Leishmaniases

- ✓ It occurs in 98 countries
- ✓ 350 million people are at risk of contracting
- ✓ 2 millions of new cases by year (WHO, 2010)
- ✓ Trypanosomatidae
- ✓ Obligate intracellular parasite



Visceral (VL)

Cutaneous (CL)

Mucocutaneous (ML)

Post-kala-azar dermal (PKDL)

Diffuse (DL)

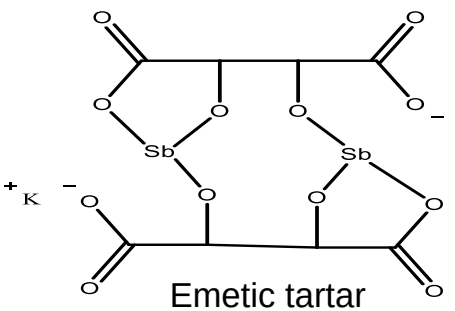
TEGUMENTARY FORMS

Current Treatment

A wide range in their efficacy

Species susceptibility

Emergence of resistant strains



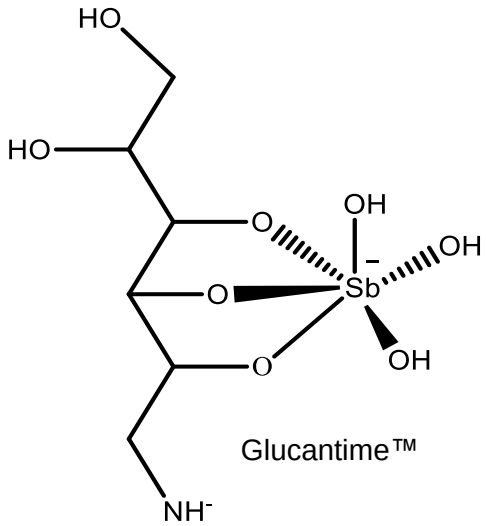
Emetic tartar


Gaspar Vianna 1912

Immune response

Differences between formulations

First line: Pentavalent antimonials



Glucantime™

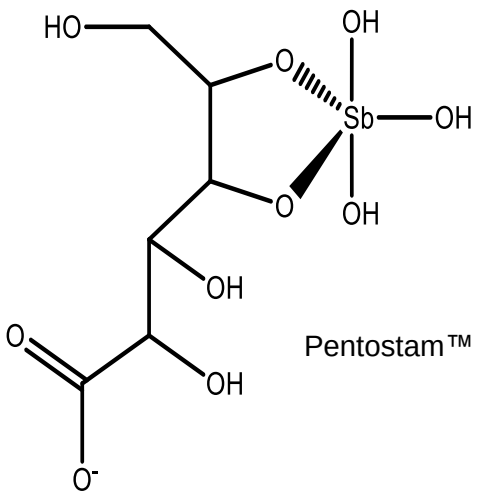
Meglumine antimoniate

Clinical Form	Daily dose	Period in days (at least)
CL	10-20mg Sb^{5+}/kg (15mg Sb/kg)	20
DL	20mg Sb^{5+}/kg	20
ML/VL/PKDL	20mg Sb^{5+}/kg	30

Alternative regimes

Intralesional

Drug combination



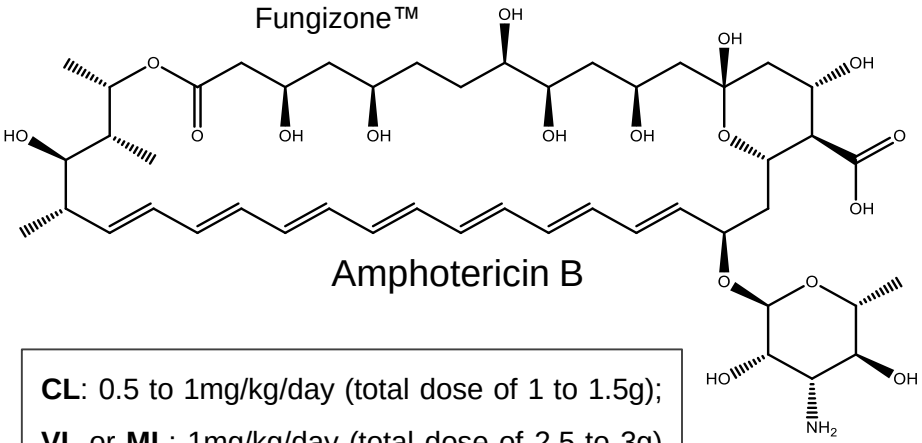
Pentostam™

Sodium stibogluconate

Treatment

Second line

Fungizone™



Amphotericin B

CL: 0.5 to 1mg/kg/day (total dose of 1 to 1.5g);
VL or **ML**: 1mg/kg/day (total dose of 2.5 to 3g) for 20 days in subsequent or alternate days.

Nephrotoxicity

Serious adverse effects

Parenteral administration

Long-term treatment

Clinical and laboratory monitoring

Most serious adverse effect

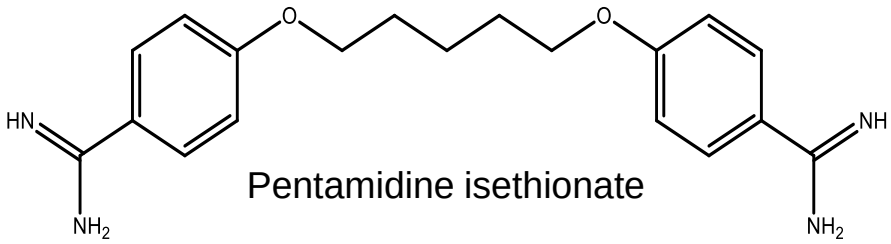
Development of insulin-dependent diabetes (5 to 12% of cases)

Contraindications

Pregnancy / diabetes mellitus

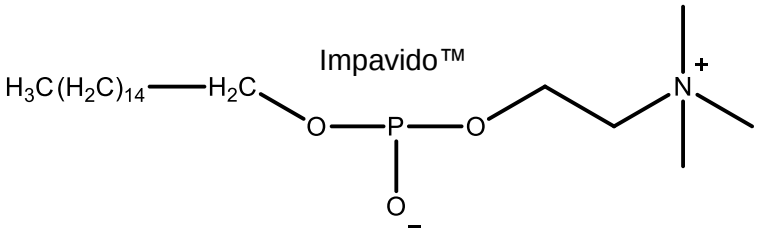
kidney / liver / heart diseases

Pentacarinat™



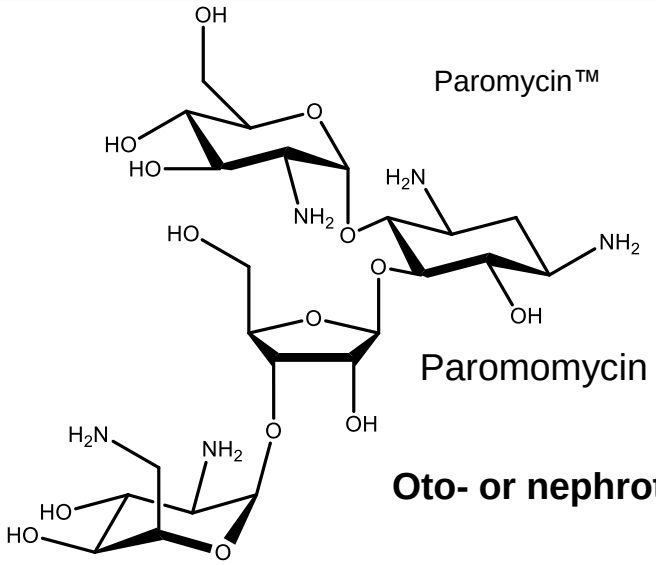
Pentamidine isethionate

Other approved drugs



Miltefosine

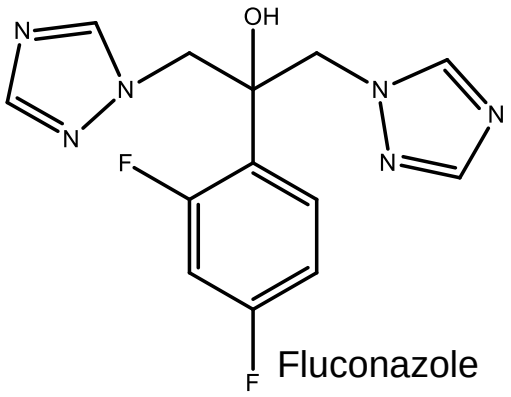
Teratogenicity!



Paromomycin

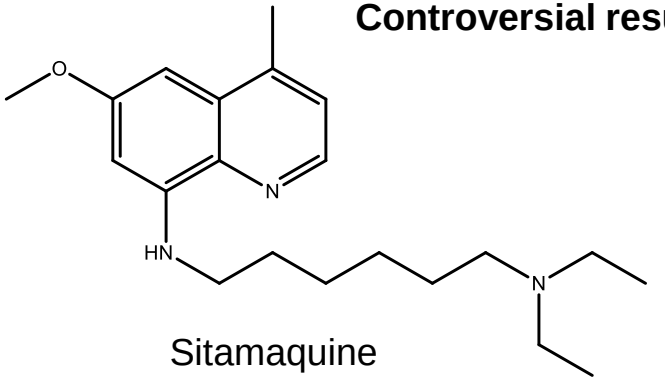
Oto- or nephrotoxicity!

Other Drugs

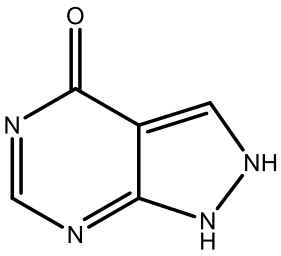


Fluconazole

Controversial results!



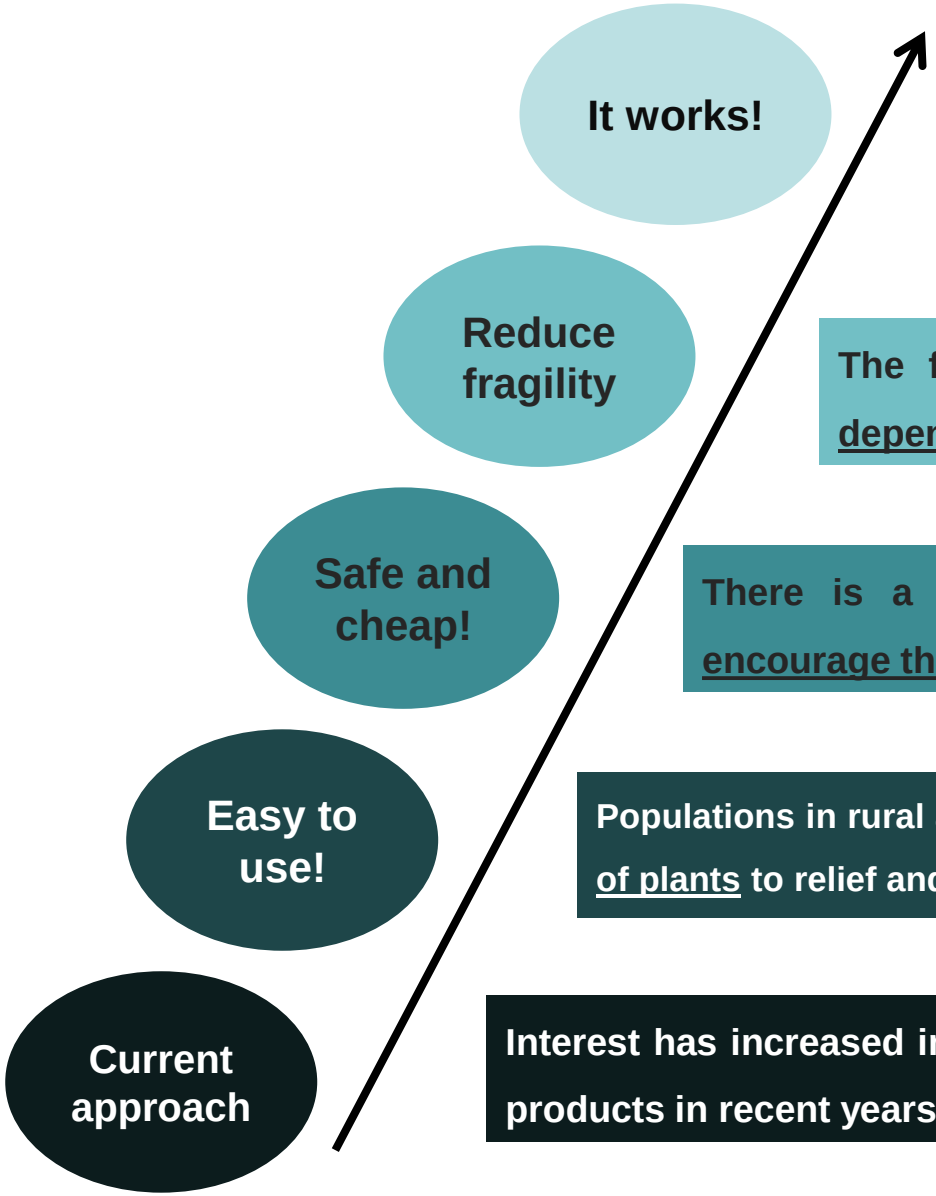
Sitamaquine



Allopurinol

New Perspective in Leishmaniases Treatment

WHY PHYTOTHERAPY AND HERBAL MEDICINES?



Extracts of medicinal plants and homologues components are effective active agents against a large array of diseases.

The focus is to promote treatments that would avoid dependency on imported drugs.

There is a number of public health programs designed to encourage the use of medicinal plants.

Populations in rural areas rely mainly on treatments based on traditional use of plants to relief and diminish symptoms associated to various diseases.

Interest has increased in applying herbal extracts, essential oils and natural products in recent years to treat diseases.

Plants with activity against *Leishmania*

Much new evidence regarding the activity of medicinal plants and their components against *Leishmania* spp has been reported

Eight plants are especially noteworthy:

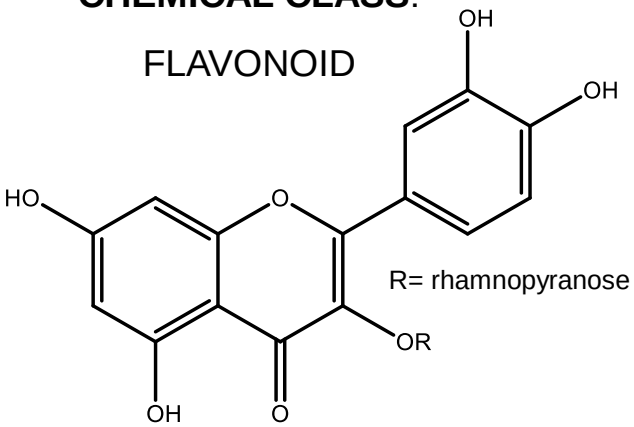
- *Kalanchoe pinnata*
- *Plumbago scandens*
- *Physalis angulata*
- *Piper aduncum*
- *Tabernaemontana australis*
- *Phyllanthus amarus*
- *Artemisia annua*
- *Tabebuia avellanedae*

Kalanchoe pinnata

https://commons.wikimedia.org/wiki/File:Starr_070308-5334_Kalanchoe_pinnata.jpg

CHEMICAL CLASS:

FLAVONOID



Quercitrin

(Quercetin-3-O-α-L rhamnopyranoside)

Characteristics: herbaceous plant or shrub, sparsely branched and reaching one meter in height.

Popular medicine:

treatment of infections, rheumatism, gastric ulcer and inflammation in general.

Assays	***Leishmania* sp**	**Results**
BALB/c mice infection (8mg/day)	*L. amazonensis*	Control of the infection similar to MA
BALB/c mice infection (400 mg/kg for 30 days)	*L. infantum*	Reduced hepatic and splenic parasite burden
Infected macrophage	*L. amazonensis*	IC_{50} 1µg/ml (macrophage toxicity: IC_{50} > 100µg/ml)
Human (215 mg/kg twice a day for 14 days)	ND	Significantly reduced lesion size only until the end of treatment.

LIKELY MODE OF ACTION: ↑**Nitric Oxide (NO)**

Plumbago scandens

http://www.cybertruffle.org.uk/vinales/eng/plumbago_scandens.htm

Characteristics: sub-evergreen shrub or climber, much branched, measuring 2-3 m in length.

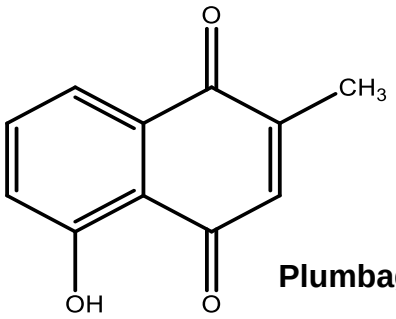
Popular medicine:

roots of *P. scandens* are used due their purgative and local anesthetic properties in the form of infusion.

Assays	***Leishmania* sp**	**Results**
Infected macrophage (plumbagin)	*L. amazonensis, L. donovani*	Growth inhibiting (1.1 µg/ml / 0.4 µg/ml)
BALB/c mice infection (2.5-5 mg/kg/day) (plumbagin)	*L. amazonensis, L. venezuelensis*	Control of the infection similar to MA

CHEMICAL CLASS:

NAFTOQUINONE



Plumbagin

(5-hydroxy-2-methyl- naftoquinone)

LIKELY MODE OF ACTION:
Inhibition of trypanothione reductase (TR)

Physalis angulata

http://keys.lucidcentral.org/keys/v3/eafrinet/weeds/key/weeds/Media/Html/Physalis_angulata_(Wild_Gooseberry).htm

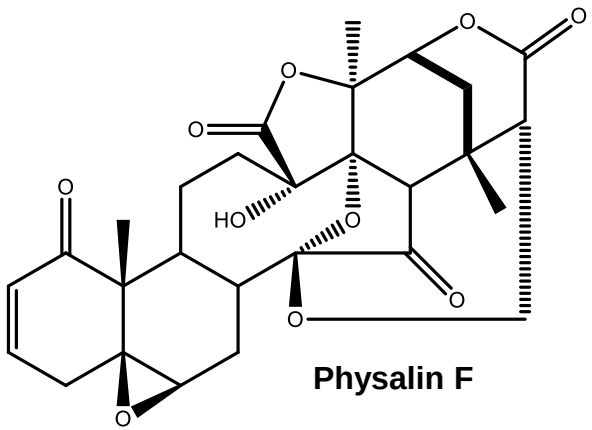
Characteristics: annual herb distributed in many countries of the tropical and subtropical regions..

Popular medicine:

It is widely used in popular medicine for the treatment of a variety of pathologies as inflammations, hepatitis, anemia, urine infection, diabetes, prostate alterations, earache.

CHEMICAL CLASS:

SECOSTEROIDS



Physalin F

Assays	***Leishmania* sp**	**Results**
Promastigotes (Physalins B, F and G)	*L. amazonensis, L. major*	Growth inhibition (IC_{50} 6.7, 1.4, e 9.2)
Infected macrophages (Physalins B and F)	*L. amazonensis, L. donovani*	Reduction in % of macrophages infected
BALB/c mice (topical 1x/day)	*L. amazonensis*	Reduction in the lesion size and parasite load

LIKELY MODE OF ACTION:
Not determined

Piper aduncum

https://pt.wikipedia.org/wiki/Piper_aduncum

Characteristics: is an upright shrub, branched, with jointed stems, 2-4m tall and native throughout Brazil.

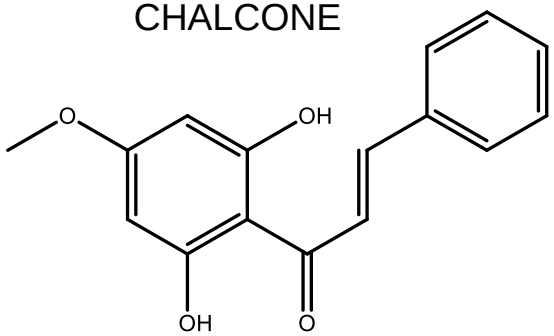
Popular medicine:

tea and alcoholic extracts of the leaves, roots and fruits are used as tonic, carminative, antispasmodic, against gonorrhea and disorders of the liver, gallbladder and spleen.

Assays	***Leishmania* sp**	**Results**
Promastigotes (Dichloromethane fraction/DMC)	*L. amazonensis*	Growth inhibition (2.2 µg/ml/ 0.5 µg/ml)
Infected macrophages (DMC)	*L. amazonensis*	Reduction of 50% in macrophages infected (40 µg/ml)
Infected macrophages (DMC at 80 µg/ml)	*L. amazonensis*	Death all of parasites

CHEMICAL CLASS:

CHALCONE



DMC

(2',6'-Dihydroxy-4'-methoxychalcone)

LIKELY MODE OF ACTION:
Inhibition of TR

Tabernaemontana australis

http://www.lookfordiagnosis.com/mesh_info.php?term=Tabernaemontana&lang=2

Characteristics: a small tree found in Brazil and other countries of South America.

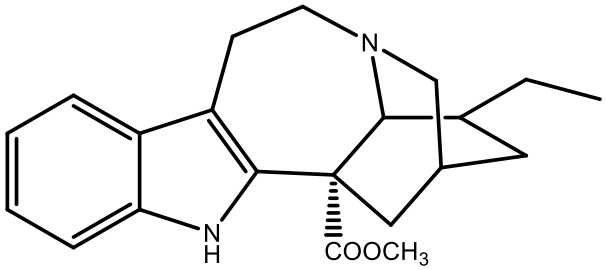
Popular medicine:

tea or infusion is used in popular medicine as an antiinflammatory, an antidote for snake bites, to relieve toothache, as a vermifuge. The essential oil of the plant leaves showed antioxidant activity.

Assays	***Leishmania* sp**	**Results**
Promastigotes (Coronaridine / chloroform fraction)	*L. amazonensis*	97% and 65%in the growth inhibition, respectively (12.5 µg/ml)
Infected macrophages (coronaridine)	*L. amazonensis*	10 and 20 µg/ml induced death to 38% and 79%, respectively.

CHEMICAL CLASS:

INDOLE ALKALOID



Coronaridine

LIKELY MODE OF ACTION:
Profound changes in mitochondria of the parasite

Phyllanthus amarus

http://www.lookfordiagnosis.com/mesh_info.php?term=Phyllanthus&lang=3

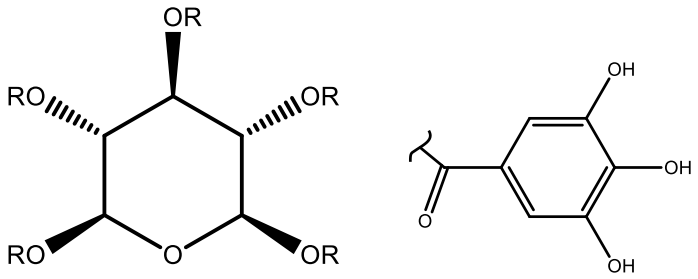
Characteristics: a common wild plant, erect, annual, branched horizontally and measuring 40-80cm. It occurs in almost all tropical regions of the world, flourishing in the rainy seasons.

Popular medicine:

eliminate kidney stones and as a diuretic. It was demonstrate its ability to relax the ureters and exert a simultaneous analgesic action.

CHEMICAL CLASS:

POLYPHENOL



Pentagalloylglucose

Assays	***Leishmania* sp**	**Results**
Infected macrophages (Gallotannins)	*L. donovani, L. major*	IC_{50} = 1–8 µM
Promastigotes (Methanolic fraction)	*L. major*	IC_{50} = 78µg/ml

LIKELY MODE OF ACTION:
↑ **TNF-α, NO and interferons**

Artemisia annua

http://nutrizioneconsapevole.altervista.org/artemisia-annua-puo-distruggere-il-98-dei-tumori/?doing_wp_cron=1442319339.1882030963897705078125

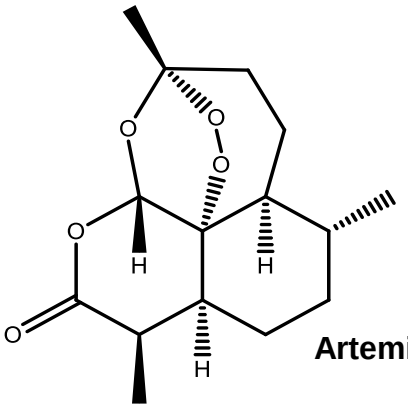
Characteristics: an annual erect, aromatic herb, from Asia and is cultivated in Brazil.

Popular medicine:

The plant has been used for centuries in traditional medicine in both China and India for the treatment of fever and lupus erythematosus. More recently, with the discovery of its antimalarial properties.

CHEMICAL CLASS:

SESQUITERPENE



Artemisinin

Assays	***Leishmania* sp**	**Results**
Promastigotes / amastigotes (Artemisinin)	*L. donovani*	Growth inhibition (IC_{50} 160 µM)
BALB/c mice (10 or 25 mg/kg/bw)	*L. donovani*	Reduction of splenic weight (220 mg to 94 and 110 mg, respectively)

LIKELY MODE OF ACTION:
Inducing apoptosis

Our expertise

http://www.ipef.br/identificacao/tabebuia.heptaphylla.asp

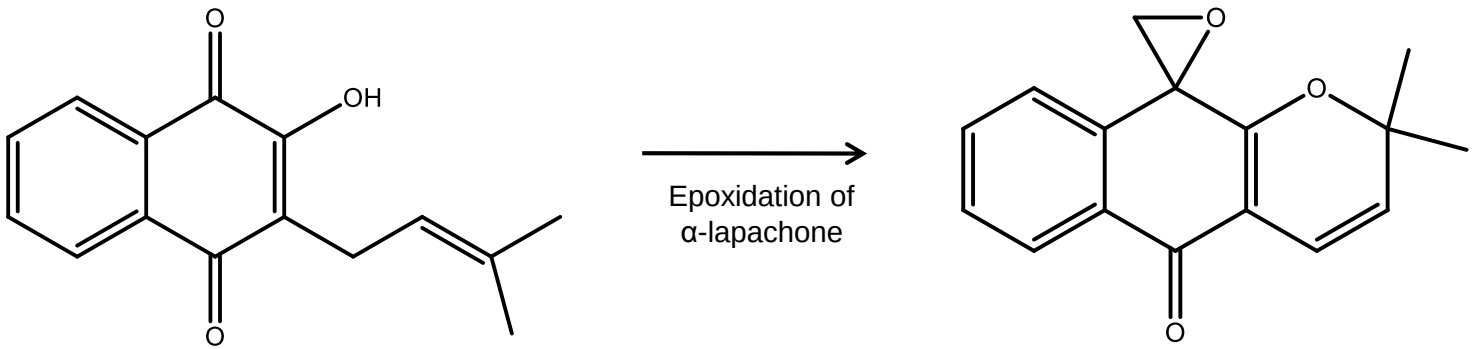
Tabebuia avellanedae

Characteristics: It is a tree of broadleaf found in forest of the Upper Uruguay, which has irregular and discontinuous distribution, occurring preferably in the depressions of land and rocky soils.

Popular medicine:

the inner bark of *Tabebuia avellanedae* is used as an analgesic, anti-inflammatory, anti-tumor and diuretic by local people in northeastern Brazil.

NAFTOQUINONES



Lapachol

Epoxi-α-lapachone

Experimental Parasitology 147 (2014) 81–84

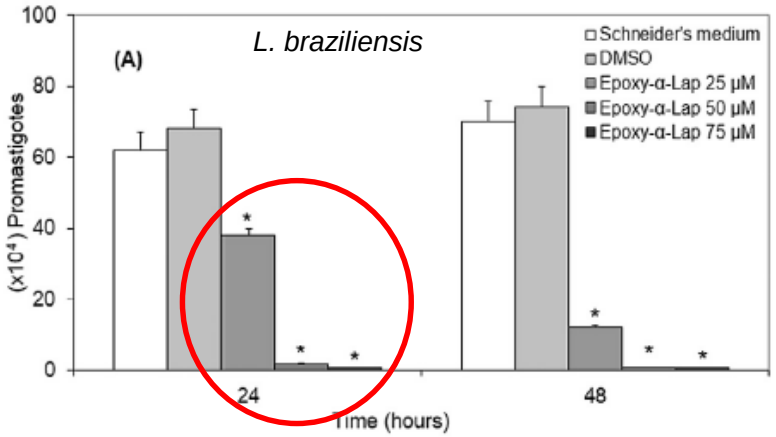
Contents lists available at ScienceDirect

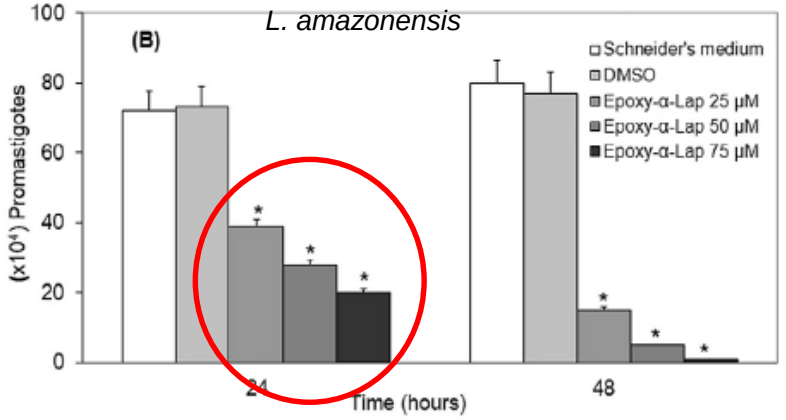
Experimental Parasitology

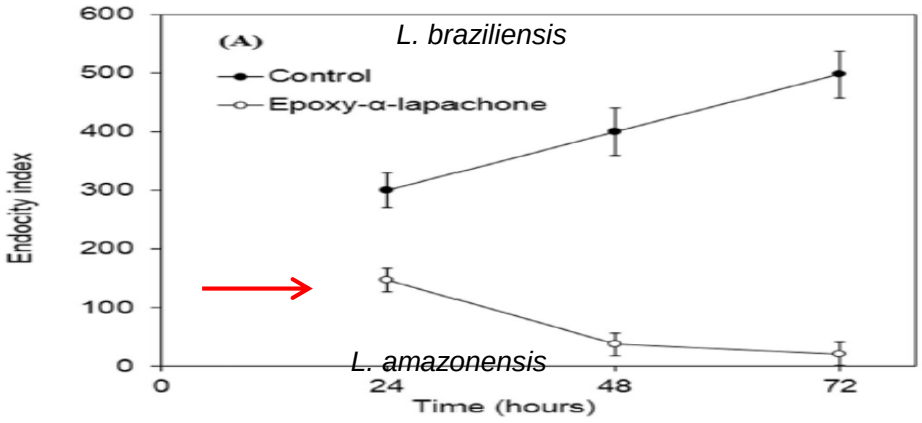
journal homepage: www.elsevier.com/locate/yexpr

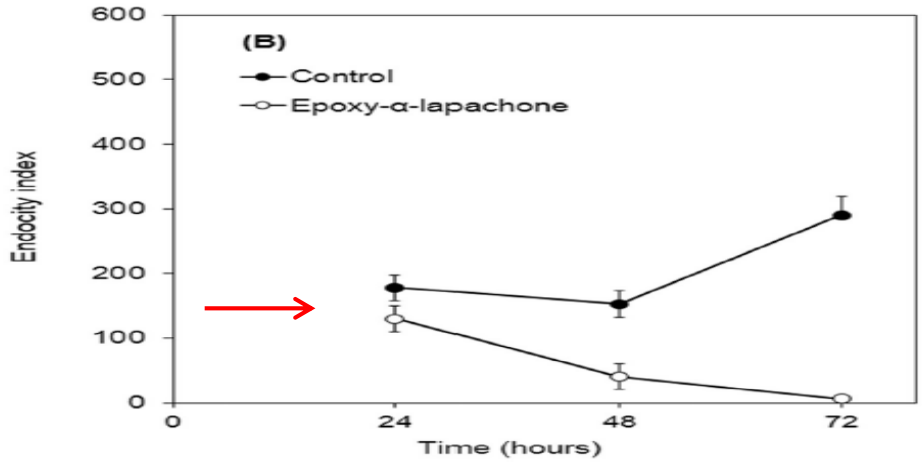
Research Brief

Evidences for leishmanicidal activity of the naphthoquinone derivative epoxy-α-lapachone









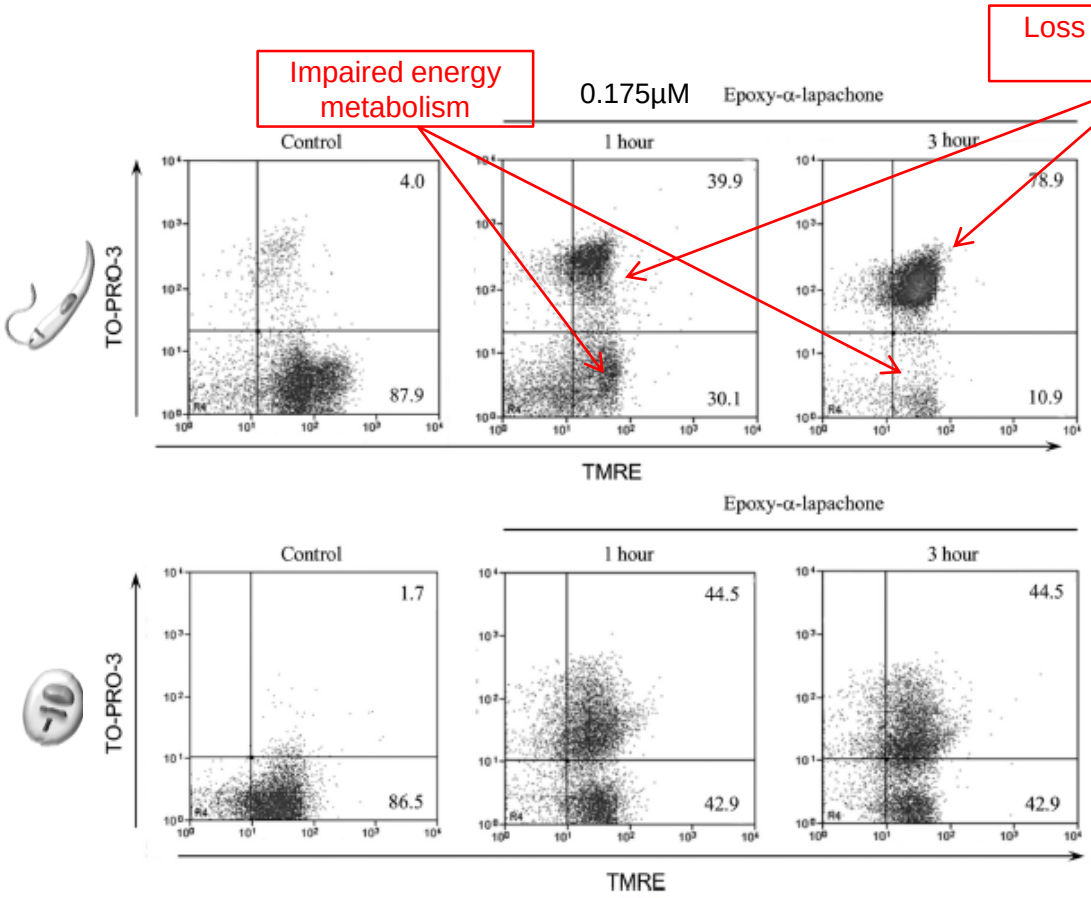
Non toxic to:
"Human macrophages"

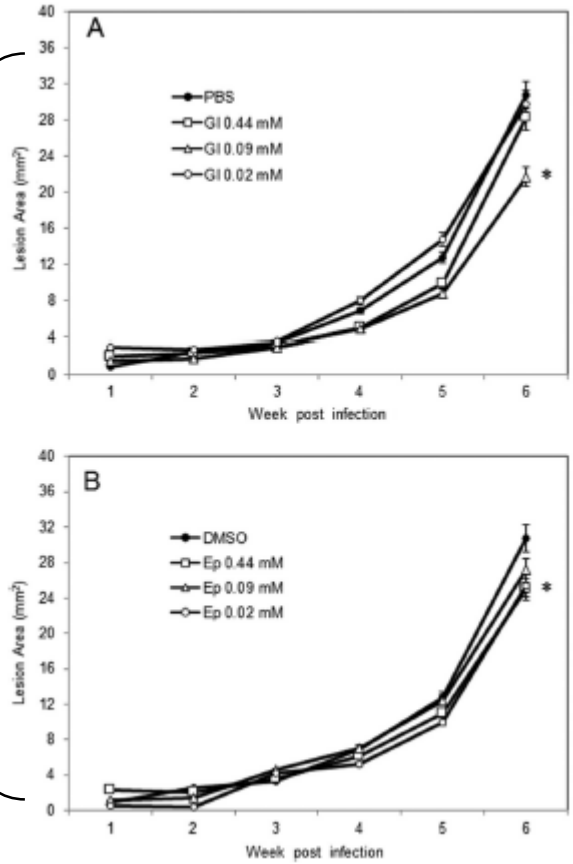
AAC Journals.ASM.org

Epoxy-α-Lapachone Has *In Vitro* and *In Vivo* Anti-*Leishmania* (*Leishmania*) *amazonensis* Effects and Inhibits Serine Proteinase Activity in This Parasite

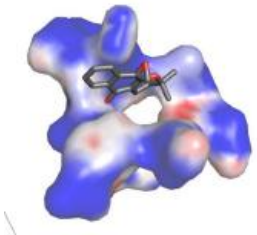
Impaired energy metabolism

Loss of membrane integrity



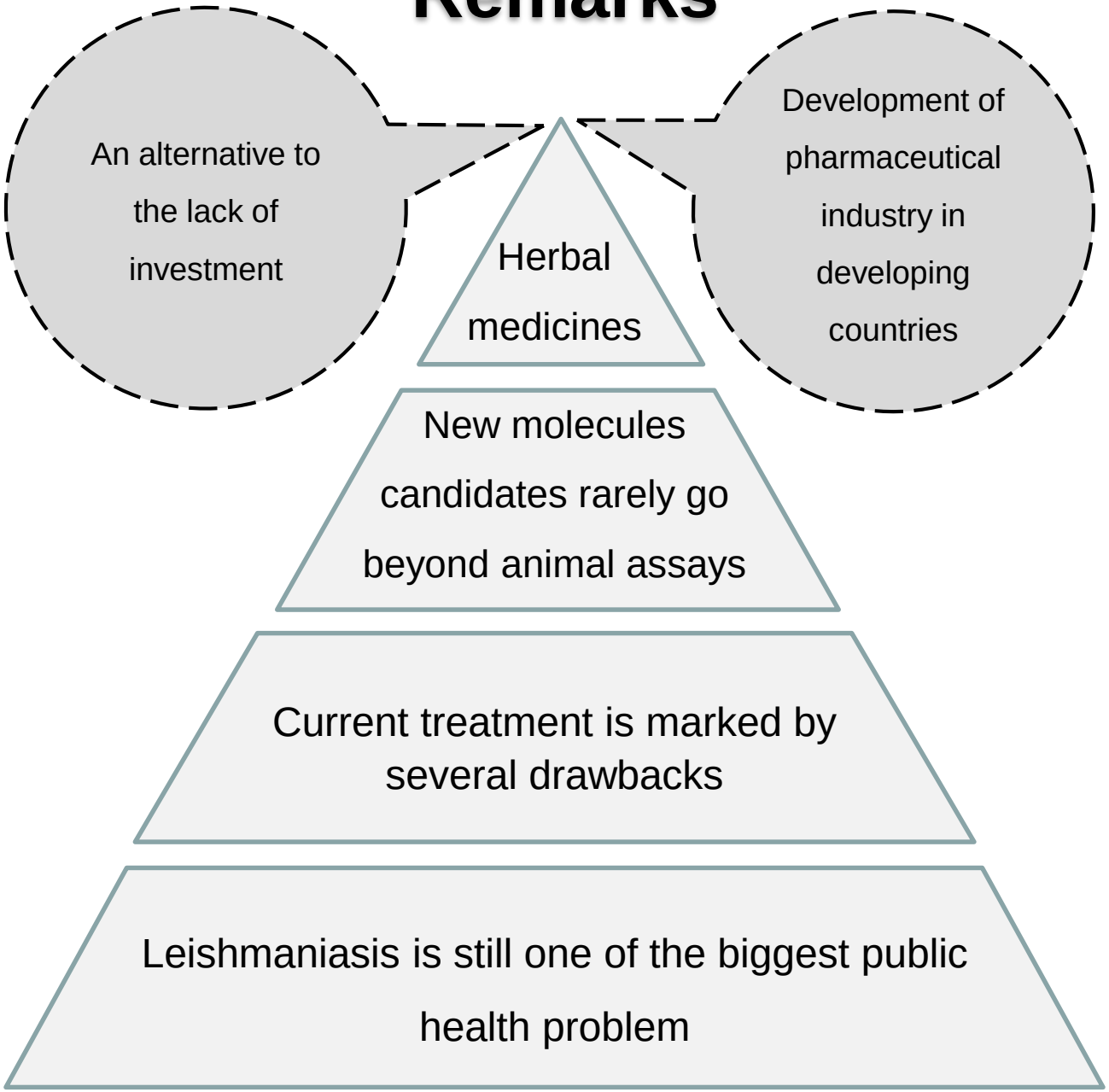


Oligopeptidase B (Serine proteinase)



inhibition of enzyme activity

Remarks


An alternative to the lack of investment
Development of pharmaceutical industry in developing countries
Herbal medicines
New molecules candidates rarely go beyond animal assays
Current treatment is marked by several drawbacks
Leishmaniasis is still one of the biggest public health problem

Partners

Benjamin Gilbert

Bernardo A. Pereira

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CNPq
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Carlos R. Alves

Franklin S.Silva

THANK YOU!

luizfilipeol07@gmail.com
luiz.filipe@ioc.fiocruz.br
+5521 38658191
+5521 38658153