

Tabebuia impetiginosa, Tabebuia avellanedae (Bignoniaceae)

English: Pink trumpet tree, lavender trumpet tree, Ipe, Taheebo

French: Poui Spanish: Pau d`arco, Ipe, Ipe roxo

German: Lapachobaum, Trompetenbaum, Feenkraut

Pharm. definition: Tabebuiae cortex

The plant

In the plant family Bignoniaceae the genus *Tabebuia* contains around 100 species from which six ones are common in Central America, 75 in West India and 25 in South America (10). Their circulation area reaches from northern Mexico and the Antilles south to northern Argentina, including the Caribbean Islands and Cuba. In the botanical system there are many synonyms and subspecies, here the name *Tabebuia impetiginosa* is used, mainly.

The plant *T. impetiginosa* is a large shrub or tree, growing to 5 to 50 m height. It is deciduous in the dry season. The leaves are in opposite pairs. The red flowers are 3 – 11 cm wide, sitting in dense clusters. The calyx is campanulate to tubular, mostly five-lobed, and looking like a trumpet. The colours of the corolla vary between the different species. The corolla of *T. impetiginosa* is pink or red. The outside of the flower tube is either glabrous or pubescent. The fruit is a dehiscent pod, 10 to 50 cm long with numerous seeds. The pods often remain on the tree through the dry season until the beginning of the rainy time.

In the tropics *Tabebuia* trees are widely used as ornamental trees in landscaping gardens, public squares and boulevards. Their floral display is very conspicuous, because many flowers appear on still leafless stems at the end of the dry season. They are useful honey plants for hummingbirds or parrots (10,36).

The green-brown wood is very tough. It is denser than water (it sinks) and has a firing rate like concrete. According to its insect resistance and durability it is popular as a decking material and for other outdoor uses.

There is a curious report about birds in the southern Pantanal (South America).

During the dry season parrots, being abundant there foraged nectar from *Tabebuia aurea* in order to obtain parts of their daily water and energy requirement. (29).

Plant parts used

The dried and shredded inner bark, the heartwood

Traditional uses

In the rain forests of South America indigenous tribes use “pau d`arco”, the inner bark of the trunk, for healing infections and against many common ailments, ranging from flu to yeast infestations and malaria, finally. They use it as tea.

In Paraguay the crude drug “tayi pyta”, derived from *Tabebuia heptaphylla* is used against wounds, inflammations and cancer (29).

In USA groups, interested in alternative methods of health by herbal use recommend “pau d`arco”, often as tea. This drug is subject of a continuing debate because of its putative anticancer activity.

Constituents

From the **leaves** iridoides and from the **flowers** antocyanes have been isolated and identified. The characteristic substances of the **inner bark** and of the **heartwood** are naphthochinones, mainly lapachol (3,6 %), lapachone, its cyclisation product and in lower concentrations (<0.01 %) coumarins and saponins (10). Lapachol and lapachone are the biologically most active substances.

The quinone pattern of the **heartwood** (80–85 % of the trunk) differs from that of the **inner bark**. Lapachol (orange needles mp 137-139°C) is the major constituent of the **heartwood** together with other anthraquinones, while furanonaphthoquinones only occur in the inner bark (32). β -Lapachone, crystallising with yellow needles (3,4-dihydro 2,2-O-dimethyl-2H naphtho-/1,2-b/pyran-5,6-dione) is a biologically very active compound.

In a investigation from the year 2006 thirteen new phenolic glycosides could be found. Most of them have a glycosyl unit, esterified by a benzoic acid derivative (34). In a further comprehensive study about the constituents of the *T. impetiginosa* **bark** twelve compounds were evaluated, four iridoid glycosides, one phenylethanoid glycoside, five phenolic glycosides, one lignan and seven known compounds (33,35). The iridoids of *Tabebuia* species are decarboxylated (17).

From the **bark** of *T. impetiginosa* two cyclopentene dialdehydes were found, too. They showed anti-inflammatory activity (12).

Quantitative determination of naphthoquinones and anthraquinones by HPLC:

Liquid chromatograph model 2249 of LKB (Pharmacia) with UV–VIS detector LKB 2141 and integrator, Rheodyn injection valve (20 μ loop), column Spherisorb ODS-2, 250 x 4 mm, particle size 5 μ , eluent water/methanol/tert, and butylether, in different mixtures, water acidified with phosphoric acid, 1 254 nm (12).

Furanonaphthochinones can be determined by the new method of micellar electrokinetic chromatography (13).

From the **bark** of *Tabebuia rosea* catalpol (specioside) was isolated. But it failed to exhibit an antimicrobial activity (8).

Volatile oil:

Volatiles were produced by steam distillation, liquid liquid extraction and analyzed by GC-MS. The major constituents were 4-methoxybenzaldehyd (52.84 μ g/g), 4-methoxyphenol (31.91 μ g/g), elemicin (5-allyl-1,2,3-trimethoxy benzene, 34.15 mg/g), trans-anethole (1-methoxy-4/1E/-1-propylbenzene, 33.75 μ g/g), and 4-methoxybenzyl alcohol, 30.29 μ g/g (23).

Preparation of tea

Two teaspoons of the dried and shredded brownish inner bark are given into 1 litre of water, cooked for 5 min and left for 15 min. It makes a bitter or sour-tasting brownish tea. Then one must drink one litre per day for 6 weeks as a medicine.

The topical use is said to be mildly anti-infective and relieving for skin disorders.

Risks of tea preparation: This application must be avoided by individuals with bleeding disorders, by pregnant and breast-feeding women, and by small children. If the extract is applied for medicinal bathing allergic reactions of the skin can appear (36)

One can order Lapacho tea: [http// Green Life Company](http://GreenLifeCompany.com)

Results of experimental studies

Effects of the aqueous extract

A survey investigation was done with the aqueous extract of *T. avellaneda* inner bark about antinociceptive and antiedematogenic effects in mice and in rats. Injuries were produced by acetic acid or formalin in mice. In both cases the nociception was reduced around 50 %. Naloxone could not reverse the effect, but caffeine did it.

In a rat oedema test the inhibition value of the aqueous extract was about 12.9 %. Authors conclude that this antinociceptive effect is associated with the adenosine system (19).

In an anti-CD-driven lymphocyte proliferation assay (MTT-assay) the aqueous extract of *Tabebuia* inner bark inhibited the lymphocyte proliferation dose dependently. In a whole blood T-cell assay the extract inhibited the ConA stimulated T-cell proliferation, dose dependently. Concentrated extracts were not toxic for lymphocytes, as verified by a trypan blue exclusion assay.

The inhibitory effects were only observed in aqueous but not in ethanol plant extracts. The authors conclude that these facts are not mediated by the lead component lapachone (3).

The water extract of Brazilian *T. avellaneda* contains two iridoids, a new phenylethanoid glycoside and further twelve known compounds. They inhibited the nitric oxide production in the lipopolysaccharide activated macrophage-like J774.1 cell (2).

Antioxidant property of the volatile oil

The antioxidant activity of the volatiles was tested in two different assays. They inhibited the formation of conjugated diene hydroperoxides at a concentration of 1000 µg/ml and the oxidation of hexenal for 40 days at a level of 5 µg/ml. The authors compare this result with the well-known antioxidants alpha-tocopherol and butylated hydroxytoluene (23).

Antibacterial and antifungal activity

The antibacterial activity of β-lapachone, 3-hydroxy-β-N-lapachone and alpha-lapachone was tested on methicillin-resistant and vancomycin-resistant *Staphylococcus* strains. The MIC values of β-lapachone were 8, 4, and 64 µg/ml, respectively. But there was no bactericidal activity for all compounds at 512 µg/ml (24).

In a paper disk diffusion assay anthraquinone-2-carboxylic acid was toxic against *Clostridium paraputrificum* with 1µg/disk, while a 100µg/disk was needed for moderate growth inhibition by lapachol. These two substances inhibited *E. coli* and *Clostridium perfringens* at 100µg/disks. According to the structure-activity relationship the C-2 position of 1,4-naphthochinones may play an important role (22). These and related substances show similar effects against *Helicobacter pylori*, compared with commonly used antibiotics like tetracyclines.

The authors conclude that these plant substances merit further studies as *Helicobacter pylori* eradicating medicines (21).

In a test line with fourteen Paraquajan plants, used in traditional medicine for the treatment of skin diseases aqueous, dichloromethane, and methanol extracts were tested in vitro against 11 fungal strains. By the agar disk diffusion methods the aqueous and methanol extracts showed the highest activity (26).

Common effects with cell cultures

An extract of *T. impetiginosa* inner bark was tested with washed rabbit platelet and cultured rat aortic vascular smooth muscle cells in vitro. N-hexane, chloroform and ethyl acetate fractions inhibited platelet aggregation induced by collagen and arachidonic acid dose dependently. The chloroform fraction inhibited cell proliferation, DNA synthesis, extracellular signal regulated kinase, and mitogen activated protein kinase (31).

Lapachol and its related compounds are toxic for eukaryotic BSC-40 African green monkey cells. But they are not toxic when applied as topic preparations on mice. Their protein synthesis was not inhibited (24).

Lapacho compounds, together with some synthetic analogues were evaluated in vitro against the growth of the human keratinocyte cell line HaCaT. The IC₅₀ value of 0.7 μ M β -lapachone showed an activity comparable to that of the antipsoriatic drug anthranile. 2-Acetyl-8-hydronaphtho(2,3-b)furan-4,9-dione, prepared in a four-step synthesis was the most potent inhibitor with an IC₅₀ value of 0.35 μ M. Other active compounds of lapachone inhibited keratinocyte growth with IC₅₀ values in the range of 0.5-3.0 μ M. However, as already observed with anthranile, remarkable damages were observed in the cell membranes, e.g. leakage of lactate dehydrogenase into the culture medium. Because of their potential activity some lapacho-derived compounds appear to be promising antipsoriatic agents (20).

Molluscicidal activity

Six ethanolic extracts from plants of the Bignoniaceae family were tested in vitro against *Biomphalaria glabra* as a test snail. Together with other ones the extract of *Tabebuia aurea* was in the median lethal concentration of 9-54 μ g/ml.

This value is below the threshold of 100 μ g/ml, a value which was set for a potential molluscicide by the WHO (30).

Twenty two derivatives of β -lapachone and related molecules were synthesized, like oxazolic, imidazolic, pyranic, and cyclopentenic ones. They were tested for their trypanocidal activity against mastigotes of *Trypanosoma cruzi*. The oxazolic and imidazolic derivatives showed a 1.5 to 34.8 time higher activity compared with crystal violet, the standard drug for sterilizing of stored blood. The author suggests, that the imidazol skeletons in the molecules corroborate the trypanocidal activity. This can be used for architectural delineation of molecules in order to get new medicines against Chagas disease (25).

Anticancer activity

Besides its inflammatory properties β -lapachone, one quinone compound from the bark of different *Tabebuia* trees was reported to have anti-cancer activities. Many investigations were done with human cell lines for finding new insights into possible molecular mechanisms, therefore.

So β -lapachone inhibits the progression and metastasis of hepatoma cell lines by inhibiting the invasive ability of the cells (11).

In human prostate carcinoma DU 145 cells lapachone induced inhibition of growth and apoptosis in dose-dependent manner as measured by MTT assay, fluorescent microscopy, and flow-cytometry analysis. Furthermore, β -lapachone markedly inhibited the activity of telomerase and the expression of human telomerase reverse transcriptase hTERT in human lung carcinoma cells (16,37). The cell growth of human prostate cancer cells is suppressed via down regulation of pRB phosphorylation and induction of Cdk inhibitor p21 (5).

In human colon cancer HCT-116 cells the apoptosis is associated with the activation of caspase-3 and the inactivation of NF-kappa B (6).

The apoptosis in Hep G2 hepatoma cell line was caused through induction of Bax and activation of the proteolysis of caspase-3 and -9, maybe (38). In human bladder cancer T24 cells the growth could be inhibited by modulation of the Bcl-2 family and the activation of caspase. The β -lapachone induced apoptosis is mediated by the mitochondrial-signalling pathway, at least in part. (15,38). Neovascularization is an essential process in tumour development. Lapachone treatment lowered the intracellular cGMP levels and the mitochondrial membrane potential, activated calpain and caspase potential. From this the endothelial cell death resulted. Addition of NO downregulated the lapachone induced cGMP depletion and protected the cells from apoptosis. Exogenous NO protects endothelial cells against the lapachone caused cell death, but not the anti-angiogenic effect. The authors believe β -lapachone is a potential anti-angiogenic drug (14). An ethanol extract of *T. barbata*, locally known as “palo de arco” to indigenous people at the upper Orinoco and Amazonas rivers, was fractionated by a brine shrimp lethality assay and column chromatography. It consisted of five naphthoquinones named lapachol 1-5 and was significantly toxic against A-549 human lung adenocarcinoma, MCF-7 human breast carcinoma, and HT-29 human colon carcinoma cells. The five isolated compounds were shown to be inhibitors of electron transport in rat liver mitochondria with IC₅₀ values in the range of 15-82.5 μ M (7).

Chemopreventive activity

In order to get better activity against cancer derivatives of lapachone were synthesized. They showed a promising new efficacy and were assayed by the National Cancer Institute (NCI, USA), especially for their binding to DNA and for their redox properties (Renou SG, Asis SE Pharmacy 2003).

Among 45 semi-synthetic derivatives of naphthoquinones, naphthoimidazole N1 was the most active one against *Trypanosoma cruzi* and its living forms. The effect on intracellular forms was 25 times higher than that for macrophages and heart muscle cells. N1 treated parasites presented an abnormal chromatin condensation and mitochondrial damage. In epimastigotes the activity of succinate C reductase was inhibited (18).

In Japan stereoselective naphthoquinones were produced chemically utilizing the Noyori reduction. The authors declare, that No 1 of these compounds shows a potent cytotoxicity against some human tumour cell lines, but less cytotoxicity against other normal human cell lines, compared with that of mitomycin (39).

Analgesic activity of naphthoquinones

The alcoholic (80 %) extract of *Tabebuia chrysotricha* heartwood, separated by column chromatography resulted lapachol, dehydro-alpha-lapachone and 5-hydroxy-2-(1'-hydroxy ethyl) naphthol/2quinones 3-b/ furan-4,9-dione.

Two groups of ten Swiss male mice (25-35 g) were given the alcoholic extract 200 mg/kg and lapachol 80 mg/kg intraperitoneally and were placed on a hot plate (50-55 C). The response time to the hot stimulus showed a very significant ($p < 0.001$) difference to the control group: Control 3.88 \pm 0.42 s, ethanol extract treated group 6.20 \pm 0.86 s, lapachol treated group 7.40 \pm 0.74 s, respectively (9).

Antifertility activity

Adult male Wistar rats were treated with 1 mL lapachol hydroalcoholic solution (100 mg/kg body weight) for 5 days and after the treatment killed after 3 and 14 days. The gamete production was not altered, but the weight of seminal vesicles was reduced significantly. According to the authors the seminal organs are the targets of the lapachol toxicity. There is a short reference about fetal mortality in female rats, too(4).

Results of clinical studies

ARQ 501 (3,4-dihydro-2,2-dimethyl-2H-naphthol /1,2-b/pyran-5,6-dione) is a fully synthetic version of β -lapachone. Combined with hydroxypropyl- beta-cyclodextrin it has successfully completed the phase I clinical trials It is currently in several phase II human clinical trials for the treatment of pancreatic cancer, head and neck cancer, and leiomyosarcoma, respectively (28).

A patient suffering from occupational asthma was submitted to a clinical evaluation with measurements of lung function, skin prick tests and specific bronchial provocation by the dust (“Ipe”) from the wood of *Tabebuia* trees. The test was positive to Ipe.

The conclusions were that the exposure to Ipe wood dust can lead to occupational asthma. The underlying mechanism could not be invented (1).

Toxicology

The dust of *Tabebuia* wood can produce asthma. The contact with it must be avoided (1)

Evaluation

In the 1970s Pau d`arco and lapachol were subjects of intensive debates because of their traditional reputation as anticancer medicines. The National Cancer Institute (NCI) of the USA investigated these ingredients in animal studies.

They were continued in human trials with lapachol in higher concentrations.

Although there was some evidence that lapachol was very active in destroying cancer cells, participants taking a therapy suffered serious side effects, like nausea, vomiting and blood problems. As a result the research into lapachol and its source, Pau d`arco was abandoned.

Critics of this investigations believe that using the therapeutic doses of Pau d`arco and not the simply isolated compound lapachol, would produce similar benefits without the potentially dangerous blood effects. It is likely that lapachol interferes with the action of Vitamin K needed for the blood to clot properly. Some researchers suggest the compounds in Pau d`arco supply some Vitamin K, so that the use of the drug would not interfere with blood clotting. Others think that lapachol together with Vitamin K supplement would make it possible for patients to take lapachol high enough to permit its potential antitumour efficacy. This should be studied furthermore.

Despite this many practitioners rely on the historical evidence of Pau d`arco`s action They often recommend it as a complement to conventional cancer treatment.

In the case of topical application of lapachol and its related substances on the skin of mice there were neither a toxic effect nor the protein synthesis was inhibited.

The topical application on the skin infected with (resistant) bacteria can be recommended, therefore.

Tabebuia impetiginosa, *T.avellanedae*

For inner use with men	---
For topical applications of the skin, infected with bacteria	**
For short-term washing of skin lesions	**
For drinking tea	*

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