Tabebuia avellanedae Lorentz ex Griseb.

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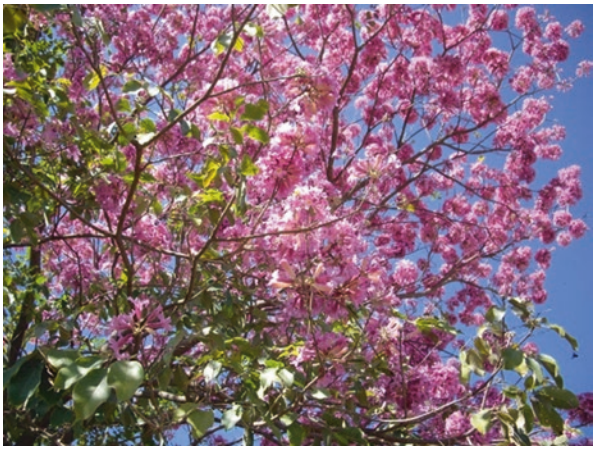

Tabebuia avellanedae Lorentz ex Grieseb.
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Abstract *Tabebuia avellanedae* Lorentz ex Grieseb. (Lapacho, Pau'd'Arco), has long been reported as used in traditional medicine in Central and Latin America for disorders as varied as leishmaniasis, bacterial infections, fever, malaria and syphilis. In the early 1960 reports of cancer being cured with Lapacho extract appeared in Brazil. The taxonomy of the genus *Tabebuia* is however complicated, and various species are used interchangeably in traditional medicine. At least *Tabebuia serratifolia* (Vahl) Nichols has to be seen as bioequivalent to *T. avellanedae*. Lapacho bark is the crude drug, in most cases prepared as infusion or tea. Lapachol and ß-Lapachol are recognized as the main bioactive compounds, and a large number of studies have focused on the anti-tumor, anti-bacterial and anti-inflammatory activity. However, so far little conclusive evidence for efficacy could be provided. The main problem of many studies had been the lack of exact taxonomic identification of the source material, the use of the wrong plant parts, and a focus of very few compounds, rather than traditional preparations. Much more research is needed to assess the actual efficacy of *Tabebuia* preparations.

Keywords Lapacho · Pau'd'Arco · *Tabebuia avellanedae* · *Tabebuia serratifolia* · Bignoniaceae

1 Taxonomic Characteristics

Tabebuia avellanedae Lorentz ex Griseb. has long been reported as "Lapacho" and "Pau d'Arco" from Latin America. The taxonomy of the species, and the genus *Tabebuia* in general is however difficult. *Tabebuia* is often linked to the genus *Tecoma* or separated into *Tabebuia* and *Handroanthus*, and most species have been described under a plethora of synonyms.

Recent taxonomic studies suggest that yellow-flowered, lapachol containing species are best recognized in their own genus, *Handroanthus* (Grose and Olmstead 2007). This, however, does not include pink-flowered lapachol containing species like *T. avellanedae*, although the species sometimes is included in *Handronanthus* nevertheless.

Tabebuia avellanedae is by far the most commonly used scientific name for the species in all but the most recent literature, and thus the older, broad concept of the genus is followed here.

Synonyms *Gelseminum avellanedae* (Lorentz ex Griseb.) Kuntze; *Handroanthus avellanedae* (Lorentz ex Griseb.) Mattos; *Tabebuia avellanedae* Lorentz ex Griseb.; *Tabebuia dugandii* Standl.; *Tabebuia impetiginosa* (Mart. ex DC.) Standl.; *Tabebuia ipe* var. *integra* (Sprague) Sandwith; *Tabebuia nicaraguensis* S.F.Blake; *Tabebuia palmeri* Rose; *Tabebuia schunkevigoi* D.R.Simpson; *Tecoma adenophylla* Bureau & K.Schum.; *Tecoma avellanedae* (Lorentz ex Griseb.) Speg.; *Tecoma avellanedae*

var. *alba* Lillo; *Tecoma impetiginosa* Mart. ex DC.; *Tecoma integra* (Sprague) Hassl.; *Tecoma ipe* var. *integra* Sprague; *Tecoma ipe* var. *integrifolia* Hassl.; *Tecoma ipe* f. *leucotricha* Hassl.

2 Crude Drug Used

The United States Food and Drug Administration (FDA) recognizes Lapacho Tea as a dietary supplement, Generally Regarded as Safe (GRAS) (FDA 1999). The pharmaceutical definition of the crude drug is Tabebuiae cortex. Lapacho bark is normally prepared as tea, although the material does need to be steeped for at least 8–10 min. Since the main compounds are not readily water-soluble (Taylor 2005). Traditionally the inner bark of the tree is used.

3 Major Chemical Constituents and Bioactive Compounds

Given the long use of the species, and the large commercial interest in particular of its use as a nutritional supplement, a large number if studies focused on elucidating the compounds of *Tabebuia avellaedae* and other species. Lapachol and ß-lapachone are regarded as the most common, and earliest isolated quinones in *Tabebuia* (Thomson 1971; de Oliveira et al. 1993).

The current list for compounds found in *Tabebuia* bark also includes acetaldehydes, alpha-lapachone, ajugols, anisic acid, anthraquinones, benzoic acids, benzenes, carboxaldehydes, chromium, chrysanthemin, dehydro-alpha-lapachone, dehydroisolapachone, deoxylapachol, flavonoids, furanonaphthoquinones, hydrochlorolapachol, 2-hydroxy-3-methyl-quinone, 6-hydroxy-mellein, iso-8-hydroxy-lariciresinol, kigelinone, lapachenol, lapachenole, various lapachones, menaquinones, 4-methoxyphenol, naphthoquinones, paeonidin-3-cinnamyl-sophoroside, phthiolol, quercetin, tabebuin, tectoquinone, vanillic acid, vanillin, veratric acid, veratric aldehyde, and xyloidone (Koyama et al. 2000a, b; Kreher et al. 1988; Lemos et al. 2007; Pertino et al. 2011; Suo et al. 2013; Steinert et al. 1995, 1996; Wagner et al. 1989; Warashina et al. 2004, 2005, 2006; Yamashita et al. 2009).

The characteristic compounds of the inner bark and the wood are naphthochochinones, mainly lapachol (3.6%), ß-lapachone, its cyclisation product and in lower concentrations (<0.01%) cumarins and saponines (10). Lapachol and lapachone are the biologically most active substances. For a complete list of compounds see Table 1.

Table 1 Characteristic compunds of Lapacho

(+)-2-(1′-Hydroxy-ethyl)-naphtho-(2,3,B)-furan-4,9-Dione	Bark
(−)-5-Hydroxy-2-(1′-Hydroxy-ethyl)-naphtho-(2,3,B)-furan-4,9-Dione	Bark
(−)-6-Hydroxy-mellein	Bark
1-(1-Hydroxy-ethyl)-Furonaphthoquinone	Bark
2-(1-Hydroxy-ethyl)-naphtho-(2–3-B)-furan-4-9-Dione	Bark
2-Acethyl-5-Hydroxy-naphtho-(2–3-B)-furan-4-9-Dione	Bark
2-Acethyl-8-Hydroxy-naphtho-(2–3-B)-furan-4-9-Dione	Bark
2-Acethyl-naphtho-(2–3-B)-furan-4-9-Dione	Bark
2-Dehydro-alpha-lapachone	Bark
2-ethyl-naphtho(2,3-B)-furan-4-9-Dione	Bark
3,4,5-Trimethoybenzoic-acid	Bark
5-Hydroxy-2-(1-Hydroxy-ethyl)-naphtho(2,3-B)-furan-4-9-Dione	Bark
6-O-(3–4-Dimethoxy-benzoyl)-ajugol	Bark
6-O-(P-Hydroxy-benzoyl)-ajugol	Bark
8-Hydroxyisolariciresinol	Bark
Anisaldehyde	Bark
Anisic-acid	Bark
Benzo[B]furan-6-Carboxaldehyde	Bark
Dehydro-alpha-isolapachone	Bark
Kigelinone	Bark
RS-8-Hydroxy-2-(1′-hydroxy-ethyl)-naphtho-(2,3,B)-furan-4,9-Dione	Bark
Vanillic-acid	Bark
Vanillin	Bark
Veratric-acid	Bark
Veratric-aldehyde	Bark
Xyloidone	Bark
Alpha-Lapachone	Bark, Wood
Beta-lapachone	Bark, Wood
Dehydro-alpha-lapachone	Bark, Wood
4-Hydroxy-benzoic-acid	Bark, Wood
Lapachenole	Bark, Wood
Lapachol	Bark, Wood
Anthraquinone-2-Aldehyde	Wood
Anthraquinone-2-Carboxylic-acid	Wood
1-Hydroxyanthraquinone	Wood
1-Methoxy-anthraquinone	Wood
2,3-Dimethyl-1,4-Naphthoquinone	Wood
2-Acetoxy-methyl-anthraquinone	Wood
2-Hydroxy-3-Methyl-anthraquinone	Wood
2-Hydroxy-methyl-anthraquinone	Wood

(continued)

Table 1 (continued)

Deoxylapachol	Wood
Lapachol-methyl-ether	Wood
Menaquinone-1	Wood
O-hydroxybenzoic-acid	Wood
Phthiolol	Wood
Quercetin	Wood
Tabebuin	Wood
Tectoquinone	Wood
P-hydroxy-benzoic-acid	Plant
chrysanthemin	Flower
Cyanidin-3-O-beta-d-rutinoside	Flower
Peonidin-3-Cinnamyl-sophoroside	Flower

4 Morphological Description

The genus *Tabebuia* includes about 100 species of large, flowering trees that are common to South American. *T. avellanedae* grows to 50 m high and the base of the tree can be 2–3 m in diameter. It is deciduous and shed its opposite leaves in the dry season. The red flowers are 3–11 cm wide, in dense clusters. The calyx is campanulate to tubular, mostly five-lobed, and trumpet-like. The corolla is pink or red. The outside of the flower tube is either glabrous or pubescent. The fruit is a dehiscent pod, 10–50 cm long with numerous seeds and often persists on the tree through the dry season to shed seeds just at the start if the rains. The wood is very hard, and denser than water.

5 Geographical Distribution

The genus *Tabebuia* belongs to the Bighnoniaceae and contains around 100 species, six of which are common in Central America, 75 in the Caribbean and 25 in South America (10). *Tabebuia* species are widely used as ornamentals in tropical landscaping.

T. avellanedae has a particularly wide distribution that ranges from Northern Mexico to northern Argentina.

6 Ecological Requirements

Many *Tabebuia* species can be classified as late succession pioneer trees, and *T. avellanedae* is no exception. The species requires full light, but has been collected from secondary humid rainforest to semi-humid forests, and is known to survive

well in pastures, where it is planted for reforestation. Specimens are known from sea-level up to about 3000 m altitude.

7 Collection Practice

For the harvest of Lapacho bark *T. avellanedae* trees sometimes felled and debarked, or simply debarked and the resulting material rasped once-twice per year (Schultes and Raffauf 1990; García-Barriga 1992). Although Lapacho collection and commerce have increased rapidly over the last decades, due to the hype about the species anti-tumor properties (Gómez Castellanos et al. 2009), *T. avellanedae* can be regarded as not threatened, its range, in fact, has expanded due to its use for reforestation.

8 Traditional Use (Part(s) Used) and Common Knowledge

T. avellanedae has been reported as being by several groups of Central and Latin American indigenous peoples to treat a wide variety of conditions, ranging from malaria, leishmaniasis, fevers, fungal and bacterial infections, to syphilis (Schultes and Raffauf 1990; Duke 1985; Duke and Vasquez 1994). The species is now mainly known by several common names in Portuguese and Spanish, and common names used in English are borrowed from South American common names. Popular common names for both species include pau d'arco (or palo de arco) (Grenand et al. 2004; Rodrigues 2006), lapacho, tahuarí (Duke and Vasquez 1994), tajibo (taheebo), and ipé (Grose and Olmstead 2007). These common names are best understood as folk genera; many species of *Tabebuia* are indicated by these names, which are not specific to *T. avellanedae,* but applied to a large variety of species with both pink and yellow flowers. Folk species may be distinguished by applying a modifying adjective to the common name. For example, Duke and Vasquez (1994) list six species of *Tabebuia,* three with an unmodified "tahuarí" as the common name, and the remaining three with an adjective in addition to "tahuarí". Although for example *Tabebuia serratifolia* (Vahl) Nichols. may be known as ipé-amarelo (Grenand et al. 2004) or pau d'arco amarelo (Jones 1995) in Portuguese, even these more specific common names may be applied to any of the 30 or more species of *Tabebuia* with yellow (amarelo) flowers. Ipé appears to be the most popular Portuguese name for *Tabebuia* spp. when they are being treated as a source of timber or as ornamentals. The name pau d'arco appears to be mostly used when medicinal uses of *Tabebuia* are considered. Boom (1990) reports the use of the bark among the Panare to treat stomachache. Muñoz et al. (2000) report its use as febrifuge by the Chacobo. The Palikur of French Guiana use the leaves to treat colds, coughs and flu, and the bark to treat leishmaniasis, dysentery, and (in a mixture with three other species) to treat diabetes. The Wayapi of French Guiana use the bark as a febrifuge (Grenand et al.

2004). Label data of an herbarium specimen at the Missouri Botanical Garden indicate that the Tacana of Bolivia use the bark to eliminate internal tumors (de Walt 1995). de Melo et al. (2011) document anti-cancer use in modern ethnomedicine.

Use is also reported among Mestizo/Creole populations. Rodrigues (2006) reports the use of *T. avellanae* bark among a Brazilian mestizo population for gastrointestinal disturbances, inflammation and tropical diseases. Grenand et al. (2004) reports French Guianese Creoles using flowers to treat colds, coughs and flu. The label data of a herbarium specimen collected by Schunke (1993), indicates the use of bark and wood in Peru to treat uterine cancer and liver cirrhosis. Another specimens, collected by Plowman (1967), reports that a bark decoction is used for "various maladies, especially cancer" in Colombia. Jones (1995) mentions use as an astringent and to treat cutaneous ulcers, and quotes a report by Wade Davis that the species is a popular cure for cancer.

There are numerous reports in the literature of the ethnomedicinal use of other species of *Tabebuia*. Given that common names such as pau d'arco represent folk generic concepts that refer to multiple scientifically recognized species, it is possible that *T. serratifolia* may be used interchangeably with other *Tabebuia* species. *Tabebuia* species are similar biochemically, so are likely to similarly efficacious (Gentry 1992). Lapachol is produced by all of the 30 species Grose and Olmstead (2007) segregates into the genus *Handroanthus.*

9 Modern Medicine Based on Its Traditional Medicine Uses

Beginning in the late 1960s, there were a number of news reports about the anticancer potential of lapachol containing species of *Tabebuia* (Jones 1995). Herbarium specimens collected by Schunke and Plowman, and Davis (as quoted in Jones 1995) all post-date the 1967 news-magazine article which Jones (1995) believes was responsible for increased interest in pau d'arco. All these species, however, belong to *Tabebuia serratifolia* (Vahl) Nichols. Gentry (1992) reported "indigenous uses of *Tabebuia* bark against cancer include that of […] *Tabebuia* in Colombia." However, the source cited by Gentry discusses the use of lapachol containing species collectively under the heading of *Tabebuia serratifolia* (or under the common name palo de arco), and notes that use of palo de arco to treat cancer had only been occurring in Colombia for about 3 years (Garcia-Barriga 1975). There is no secure indication whatsoever that indeed *T. avellanedae* was the species that first entered into modern medicinal practice based on traditional use.

Modern research on the medicinal properties of *Tabebuia* goes back to the 1960s when the US National Cancer Institute started a large scale global plant screening program in order to isolate new anti-cancer compounds (Cragg and Newman 2005). One of the compounds of interest turned out to be lapachol, isolated from *T. avellanedae* (Cassady and Douros 1980). Gómez Castellanos et al. produced a review of earlier medicinal research on Lapacho (2009).

A variety of authors found scant anti-cancer efficacy of *Tabebuia* compounds. de Santana et al. (1968) were the first team to report anti-cancer activity. Choi et al. (2003) report on efficacy of ß-lapachone against prostate cancer by down-regulating pRB regulation and Cdk inhibitor p21 induction. de Sousa et al. (2009)and Costa et al. (2011) found lapachol and other compounds as tumor inhibitor in *Drosophila*, while Queiroz et al. (2008) and Higa et al. (2011) documented activity in mice, and Moon et al. (2010) and Inagaki et al. (2013) produces cytotoxicity against leukemia cells. Kim et al. (2007) found anti-invasive and anti-metastatic properties of ß-lapachone, while a general antitumor effect of the molecule was reported by a variety of teams (Lamberti et al. 2013, Lee et al. 2005, 2006, 2012, 2013). Mukherjee et al. (2009) produced growth inhibition of human estrogen receptors in breast cancer cells by applying *Tabebuia* extract. Finally, tumor apoptosis was shown by Woo and Choi (2005), Woo et al. (2006), and Yamashita et al. (2007).

Although most research focused on anti cancer properties, some teams found indication of activity in other areas such anti-oxidant activity (Awale et al. 2005; Moreira Vasconcelos et al. 2014; Park et al. 2003); immuno-stimmulation (Böhler et al. 2008); anti-inflammatory effects (Byeon et al. 2008; Lee et al. 2012); wound-healing (Coelho et al. 2010; Kung et al. 2008; Suo et al. 2012); anti-depressant (Freitas et al. 2010, 2013); anti-vascular (Garkavtsev et al. 2011); anti-leishmanial (González-Coloma et al. 2012; Menna-Barreto et al. 2005); anti-bacterial (Höfling et al. 2010; Macedo et al. 2013; Machado et al. 2003; Moreira Vasconcelos et al. 2014; Park et al. 2006; Pereira et al. 2006); anti-triglyceric (Kiage-Mokua et al. 2012); larvicidal (Kim et al. 2013); anti-fungal (Melo e Silva et al. 2009); anti-ulcer (Pereira et al. 2013; Twardowschy et al. 2008), molluscididal (Silva et al. 2007), reduction of autoimmune effects (Xu et al. 2013)

Toxic effects explaining anti-conceptive properties were found by de Cássia da Silveira and de Oliveira (2007), de Miranda et al. (2001), Lemos et al. (2012), and Moreira Vasconcelos et al. (2014).

10 Conclusions

Based on the above stipulations, it is evident that *T. avellanedae*, as well as other species like *Tabebuia serratifolia*, are known by several common names, all of which may also be applied to other species of *Tabebuia.* Referring to all these species as “pau d’arco” or “lapacho” reflects traditional folk taxonomy. There are a variety of reported ethnomedicinal uses for various species. The earliest reports of traditional medicinal use most likely refer to *Tabebuia serratifolia* (Vahl) Nichols. Many other species of *Tabebuia* are also used medicinally, and various scientifically recognized species with similar biochemistry may be used interchangeably under the folk concept of “pau d’arco” and “lapacho”. From a scientific perspective the uses as well as vernacular names of *Tabebuia serratifolia* (Vahl) Nichols. are entirely interchangeable with the uses and traditional names of *T. avellanedae* Lorentz ex Griseb.

Although lapachol and ß-lapachol are recognized as the main bioactive compounds, and a large number of studies have focused on anti-tumor, anti-bacterial and anti-inflammatory activity, so far little conclusive evidence for efficacy could be provided. The main problem of many studies had been the lack of exact taxonomic identification of the source material. In addition, many studies focused on material consisting of any woody part of the tree, rather than the inner bark layer that is reported in traditional use. The focus on very few compounds regarded as bioactive, rather than traditional preparations, might also have had serious effects on efficacy. Much more research is needed to assess the actual efficacy of *Tabebuia* preparations.

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