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Lapachol and its congeners as anticancer agents: a review

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Abstract Lapachol is a naturally occurring 1,4-naphthoquinone originally isolated by the Italian phytochemist E. Paterno from *Tabebuia avellanedae* (Bignoniaceae) in 1882 and subsequently found in several other genera belonging to the families of Leguminosae, Malvaceae, Plumbaginaceae, Lamiaceae, Arecaceae, Scrophulariaceae, Verbenaceae, Celastraceae, Avicenniaceae, Caesalpiniaceae, Rubiaceae, and Proteaceae. A wide range of pharmacological activities have been observed for lapachol and its semi-synthetic derivatives in the literature, such as antileishmanial, anticarcinomic, anti-inflammatory, antimalarial, antiseptic, antitumor, antiviral, bactericidal, fungicidal, insectifugal, pesticidal, schistosomicidal, termiticidal, and viricidal effects. The aim of this review is to discuss in detail the phytochemical properties and pharmacological effects of the title compound that have been reported thus far, highlighting its potential therapeutic benefits for the future.

Keywords Bignoniaceae · Lapachol · 1,4-Naphthoquinones · Anticancer activity

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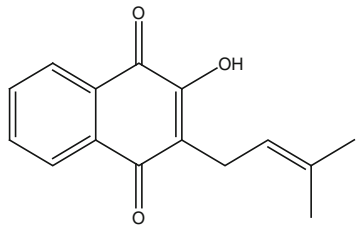
Historical introduction of lapachol

1,4-Naphthoquinones represent a large class of natural compounds and are found in a wide range of plant families as well as in fungi and bacteria. Notable examples of naturally occurring 1,4-naphthoquinones include the K vitamins, juglone (isolated from the black walnut, *Juglans nigra* L. [Juglandaceae]), and plumbagin (obtained from *Plumbago*, *Drosera*, and *Nepenthes* spp.). Naphthoquinone derivatives have valuable pharmacological effects, acting as cytotoxic, antibacterial, antifungal, antiviral, antiprotozoal, insecticidal, anti-inflammatory, and antipyretic agents (Grolig and Wagner 2005). Atovaquone® (**2**), a derivative of lapachol (**1**), has been approved for the treatment of *Pneumocystis pneumonia*, toxoplasmosis, and malaria (Eyong et al. 2008). This latter was also tested as anti-tumor agent by the National Cancer Institute (Bethesda, MD, USA) in the 60-cell-line panel under the NSC-759582 NCI code, but displaying a poor activity ranging from a minimum percentage of inhibition of 75.5 % against UO-31 to a maximum of 122.4 % against RXF 393 renal cancer cell lines.



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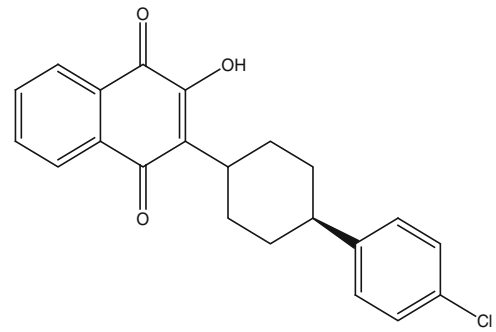

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The mechanisms of action underlying the observed effects of naphthoquinone derivatives are mainly due to their capacity to interact with topoisomerases and to generate semiquinone radicals and reactive oxygen species (ROS) inside the cell (da Silva et al. 2003). Plants containing naphthoquinones are widely used in Southeast Asia and South America to treat malignant and parasitic diseases. In this context, lapachol **1** (2-hydroxy-3-isopentenyl-1,4-naphthoquinone) represents one of the best examples of a research trend in phytochemistry.

Lapachol was first isolated in 1882 by the Italian chemist Emanuele Paternò from the tree *Tabebuia avellanedae* Lorentz ex Griseb. (Bignoniaceae) (Paternò 1882). Its name is derived from the term "lapacho," the name by which this plant is commonly known in Brazil, where it is also called "pau d'arco" and "taheebo." Extracts of the inner bark of *T. avellanedae*, from which lapachol was first purified, are used by local populations as analgesic, anti-inflammatory, anti-neoplastic, antimicrobial, and diuretic agents (Miranda et al. 2001). The compound was first named "lapachic acid" by Paternò because of its fairly acidic properties, and the term "lapachol" was assigned by Hooker (1892). In 1927, Fieser definitively confirmed the structure of **1** by comparing an authentic sample extracted from the bark of *T. avellanedae* with one obtained by chemical synthesis (Fieser 1927).

Natural sources of lapachol

Several plants in the Bignoniaceae family are the richest sources of lapachol. However, this natural naphthoquinone has been also extracted from genera of the families Leguminosae, Malvaceae, Plumbaginaceae, Lamiaceae, Arecaceae, Scrophulariaceae, Verbenaceae, Celastraceae, Avicenniaceae, Caesalpiniaceae, Rubiaceae, and Proteaceae, as outlined in Table 1.

Screening of lapachol in plant extracts

Several methods are currently available to detect the presence of lapachol in vegetable extracts. The absorption spectra of the title compound were first fully described in Cooke et al. (1939). In the early 1960s, experimentation with the use of lapachol for therapeutic purposes prompted the search for alternative and more sensitive methodologies to accurately measure the concentration of compound **1** not only in plant extracts but also in biological fluids. In 1969, a fluorimetric method for the determination of lapachol in serum was developed by Finkel and Harrison (1969). These authors exploited the capacity of compound **1** to fluoresce at 410 nm after reduction with $NaHSO_3$, leading to a highly sensitive analytical technique. Then, Dawson et al. (1989) provided the complete NMR assignment and interpretation of lapachol, using one- and two-dimensional techniques. The IR behavior of **1** was well studied by Farfan et al. (2006). These authors were able to accurately calculate and assign all vibration frequencies of lapachol, even in enriched plant extracts, using the density functional theory. Currently, the most widespread and frequently used technique for the qualitative and quantitative analysis of compound **1** in complex matrices is high-performance liquid chromatography (HPLC). The first report of the use of this technique in the literature was provided by Awang et al. (1986). These authors

Table 1 Main natural sources of lapachol

Sources	References
Abutilon pakistanicum Jafri and Ali in Jafri (Malvaceae)	Bakhat et al. (2010)
Acacia jacquemontii Benth. (Leguminosae)	Singh et al. (2010)
Acacia nilotica (Linn.) Del. (Leguminosae)	Prakash and Garg (1981)
Austroplenckia populnea var. *Ovata* (Reissek ex Mart.) Lundell (Celastraceae)	De Sousa et al. (2006)
Avicenna alba Blume (Avicenniaceae)	Ito et al. (2000)
Avicennia tomentosa Jacq. (Avicenniaceae)	Bournot (1914)
Bauhinia guianensis Aubl. (Caesalpiniaceae)	Viana et al. (1999)
Bignonia gracilis Lodd. (Bignoniaceae)	Prakash and Singh (1980a, b, c)
Bignonia leucoxylon L. (Bignoniaceae)	Oesterde (1917) and Oesterde (1916)
Bignonia unguiscati Bureau and K.Schum. (Bignoniaceae)	Joshi et al. (1985)
Capraria biflora L. (Scrophulariaceae)	Lemos et al. (2007)
Catalpa longissima Sims (Bignoniaceae)	Chauhan et al. (1988)
Conospermum spp. (Proteaceae)	Cannon et al. (1975)
Desmodium pulchellum (L.) Benth. (Fabaceae)	Joshi et al. (1975)
Diphysa robinoides Benth. (Fabaceae)	Sagrero-Nievese (1986)
Dolichandrone crispa Seem (Bignoniaceae)	Prakash and Singh (1980a, b, c)
Euterpe precatoria Mart. (Arecaceae)	Galotta et al. (2008)
Heterophragma adenophyllum Seem ex Benth. and Hook. F. (Bignoniaceae)	Singh et al. (1972, 2006) and Joshi et al. (1979)
Hibiscus tiliaceus L. (Malvaceae)	Ali et al. (1980)
Jacaranda mimosaefolia D. Don (Fabaceae)	Joshi et al. (1975)
Kigelia tipulat (Lam.) Benth. (Bignoniaceae)	Khan and Mlungwana (1999)
Kigelia pinnata (Jacq.) DC (Bignoniaceae)	Singh et al. (2010), Joshi et al. (1981) and Govindachari et al. (1971)
Lippia microphylla Cham. (Verbenaceae)	Lemos et al. (2007)
Lippia sidoides Cham. (Verbenaceae)	Lemos et al. (2007)
Lomatia illicifolia R.Br. (Proteaceae)	Rennie (1895)
Lomatia longifolia R.Br. (Proteaceae)	Rennie (1895)
Macfadyena unguis-cati (L.) A.H.Gentry (Bignoniaceae)	Duarte et al. (2000)
Mansoa spp.(Bignoniaceae)	Zoghbi et al. (2009)
Markhamia hildebrandtii (Baker) Sprague (Bignoniaceae)	Chen and Lee (1986)
Markhamia platycalyx Sprague (Bignoniaceae)	Joshi et al. (1985)
Markhamia tipulate Wall (Bignoniaceae)	Singh and Singh (1980) and Joshi et al. (1978)
Markhamia zanzibarica K. Schum. (Bignoniaceae)	Khan and Mlungwana (1999)
Melloa quadrivalvis (Jacq.) A. H. Gentry (Bignoniaceae)	Lima et al. (2005)
Millingtonia hortensis Linn. (Bignoniaceae)	Prakash and Garg (1981) and Singh et al. (1972)
Newboldia laevis (P. Beauv.) Seemann ex Bureau (Bignoniaceae)	Eyong et al. (2005, 2006) and Houghton et al. (1994)
Oroxylum indicum (L.) Benth. Ex Kurz (Bignoniaceae)	Joshi et al. (1977a, b, c, d)
Paratecoma peroba (Record) Kuhlm (Bignoniaceae)	Sanderman et al. (1968)
Paulownia kawakamii T. Ito (Scrophulariaceae)	Huang et al. (2004)
Phyllarthron comorense DC (Bignoniaceae)	Joshi et al. (1973a, b, 1975, 1976)
Plumbago scandens L. (Plumbaginaceae)	Rodrigues et al. 2006.
Plumbago zeylanica L. (Plumbaginaceae)	Kishore et al. (2010)
Radermachera sinica Hemsl. (Bignoniaceae)	Inoue et al. (1981)

Table 1 continued

Sources	References
Radermachera xylocarpa K. Schum. (Bignoniaceae)	Shetgiri et al. (2001)
Randia dumatorium L. (Rubiaceae)	Joshi et al. (1981)
Rubia tinctorum L. (Rubiaceae)	Kawasaki et al. (1992)
Salvia sahendica Boiss and Buhse(Lamiaceae)	Jassabi et al. (2006)
Stereospermum kunthianum Cham. (Bignoniaceae)	Ghogomu-Tih et al. (1986)
Stereospermum personatum (Hassk.) Chatterjee (Bignoniaceae)	Kumar et al. (2005)
Stereospermum suaveolens DC. (Bignoniaceae)	Joshi et al. (1977a, b, c, d)
Stereospermum tetragonum DC (Bignoniaceae)	Purushothaman and Natarajan (1974)
Tabebuia avellanedae Lorentz ex Griseb. (Bignoniaceae)	Viana et al. (2003), Krustrak (2001), Wagner et al. (1989), Burnett and Thomson (1967) and de Lima et al. (1962)
Tabebuia chrysantha (Jacq.) G.Nicholson (Bignoniaceae)	Burnett and Thomson (1968)
Tabebuia chrysotricha (Mart. Ex DC.) Standl. (Bignoniaceae)	Grazziotin et al. (1992)
Tabebuia coralibe Standl. (Bignoniaceae)	Rodriguez, et al. (1999)
Tabebuia flavescens Benth. and Hook.f. ex Griseb. (Bignoniaceae)	Orth (1960)
Tabebuia guayacan Hemsl. (Bignoniaceae)	Manners and Jurd (1976)
Tabebuia heptaphylla (Vell.) Toledo (Bignoniaceae)	Schmeda-Hirschmann and Papastergiou (2003)
Tabebuia impetiginosa (Mart. Ex DC.) Standl. (Bignoniaceae)	Gomez Castellanos et al. (2009)
Tabebuia ochracea (Cham.) Standl. (Bignoniaceae)	Zani et al. (1991)
Tabebuia palmeri Rose (Bignoniaceae)	Villegas et al. (1995)
Tabebuia pentaphylla Hemsl. (Bignoniaceae)	Rohatgi et al. (1983), and Prakash and Singh (1980a, b, c, 1981)
Tabebuia rosea DC (Bignoniaceae)	Girard et al. (1988) and Joshi et al. (1973a, b, 1976, 1977a, b, c, d)
Tabebuia serratifolia Vahl. Nicholson (Bignoniaceae)	Lemos et al. (2007), Velasquez et al. (2004) and Vidal-Tessier et al. (1988)
Tecoma stans Juss. (Bignoniaceae)	Dohnal (1976)
Tecomella undulata Seem (Bignoniaceae)	Singh et al. (2008a, b), Joshi et al (1977a, b, c, d, 1986), Joshi and Singh (1974) and Gupta et al. (1969)
Tectona grandis L.f. (Lamiaceae)	Lukmandaru et al. (2009), Singh et al. (1989, 2008a, b), Moreira et al. (2006), Windeisen et al. (2003), Khan and Mlungwana (1998) and Sandermann and Simatupang (1964, 1965)
Zeyheria digitalis (Vell.) L.B. Sm. and Sandwith (Bignoniaceae)	da Silveira et al. (1975)
Zeyheria montana Mart. (Bignoniaceae)	Jacome et al. (1999)

developed a sensitive screening technique for lapachol using a reverse-phase HPLC with a Brownlee RP-18 Sheri-10 column and MeCN (aq) 0.25 %–AcOH 1:1 as the mobile phase. The HPLC separation of **1** in mixtures containing structurally similar products was reported about 10 years later by Steinert et al. (1996) using an isocratic elution and by Novotna et al. (1999). An alternative reversed-phase methodology, using a LiChrosorb RP-10 column and MeOH (aq) 5 %—AcOH 8:2 as the elution mixture, has been recently described by Fonseca et al. (2004). Mass spectrometry represents the most recently described method for the analysis of lapachol in plant extracts. The fragmentation study and the electrospray ionization mass spectrometry of lapachol were thoroughly reported in Vessecchi et al. (2010). These authors studied the occurrence of protonated and carbocationic species in the positive mode and deprotonated species in the

negative ones using collision-induced dissociation experiments. Another very sensitive technique, full-scan high resolution mass spectrometry, was also used for the analysis of lapachol in food, feed, and general botanicals (Mol et al. 2011). Finally, alternative methodologies, such as voltammetry (Ngameni et al. 2000) and thermal analysis (Santan et al. 2008), have also been recently used for the same purposes.

Physicochemical properties of lapachol and synthetic methodologies

Lapachol is a light to dark yellow crystalline powder that typically forms prisms with a pKa of 6.15 (Ossowski et al. 2008) and that has a melting point of 141–143 °C. Lapachol is fairly soluble in water, although its solubility is greatly affected by pH; the solubility ranges from 1.5 μg/mL at pH 4.0–5 mg/mL at pH 10. The UV absorption maxima of lapachol are 251, 278, and 331 nm. As a bidentate ligand, lapachol tends to form stable complexes with transition metals such as copper, iron (Sawhney et al. 1983), zinc, cobalt (Martinez et al. 2005), nickel (Farfan et al. 2009), bismuth, antimony (de Oliveira et al. 2011), and several others (Bhatia and Vohra 1982). The previous and renewed interest in lapachol from the phytochemical and pharmacognostic points of view prompted the development of several synthetic processes to synthesize this biologically active naphthoquinone. As stated above, in 1892, Hooker described the first method to obtain lapachol by the reaction of isovaleraldehyde and 1,4-naphthoquinone (Hooker 1892). Subsequently, in 1927, Fieser obtained the title compound by reacting the silver salt of 2-hydroxy-1,4-naphthoquinone (lawsone) with 3,3-dimethylallyl bromide as the alkylating agent, producing **1** with a very low yield (5 %) (Fieser 1927). Approximately 40 years later, Pettit and Houghton described a synthetic scheme by which lapachol was obtained using a six-step process starting from lawsone and succinyl peroxide followed by a series of reductions and Grignard reactions (Pettit and Houghton 1971). At almost the same time, Jacobsen and Torssel applied the alkylation of quinones with radicals obtained from the decarboxylation of carboxylic acid promoted by peroxydisulfate ions to lawsone (Jacobsen and Torssell 1973). A Williamson etherification followed by a heat-promoted Claisen rearrangement was employed to synthesize **1** from lawsone and 3,3-dimethylallyl bromide. In Sun et al. (1998) alkylated the lithium salt of the lawsone nucleophile with 3,3-dimethylallyl bromide, providing lapachol in 40 % yield. Finally, in recent years, Kazantzi et al. (2007) used the Pd-catalyzed allylation of lawsone with isopentenyl alcohol or isopentenyl methyl ether to synthesize **1** with good yield, and Ferreira et al. (2011) similarly used the formic acid–water mediated one-pot reduction of *o*-quinone methides. Lapachol is easily oxidized both in vitro and in vivo. The redox transformations of the title compound are currently of great interest because they are believed to be partly responsible for the observed biological effects of lapachol. For these reasons, simple in vitro methods to mimic the bioxidation process of **1** have recently been established. A Mn(III) complex with H_2O_2 and hypervalent iodine species has been used to investigate and structurally characterize the chemical entities derived from the total or partial oxidation of lapachol (Niehues et al. 2012a, b; Pires et al. 2011; Bodini and Arancibia 1989).

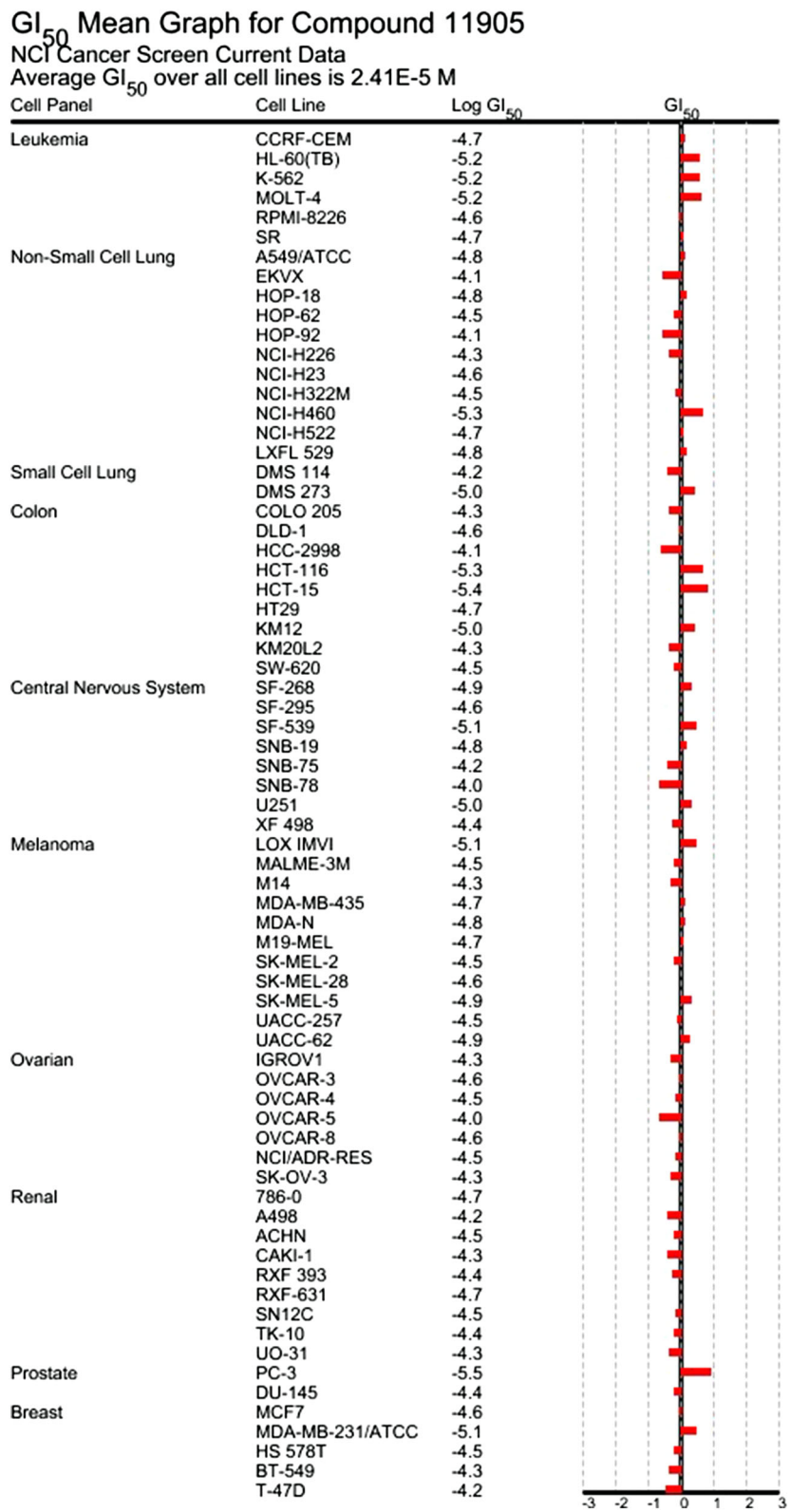
In vitro pharmacological and toxicological analyses of the antitumor activity of lapachol

Numerous lapachol derivatives have already been synthesized and have been shown to exert significant in vitro growth inhibitory effects in various cancer cell lines. The antitumor activity of lapachol was first described in the early 1970s (Block et al. 1974), and this compound was tested by the National Cancer Institute (Bethesda, MD, USA) in the 60-cell-line panel under the NSC-11905 NCI code (Fig. 1).

The mean in vitro growth inhibitory concentrations shown in Fig. 1 indicate that the 60 cancer cell lines analyzed show only small differences in lapachol sensitivity at the micromolar concentrations tested. Lapachol has also been demonstrated to reduce the number of tumors caused by doxorubicin in *Drosophila melanogaster* heterozygous for the tumor suppressor gene *wts* (Costa et al. 2011).

In addition to its antiproliferative activity in cancer cells, lapachol also decreases the invasion of HeLa cells and could therefore represent an interesting scaffold with which to generate novel anti-metastatic compounds (Balassiano et al. 2005). Lapachol-

Fig. 1 The data illustrate the average 50 % growth inhibitory concentrations obtained for lapachol in a panel of 60 cancer cell lines. The testing was performed by the Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute. The URL to the Program's website is http://dtp.cancer.gov. These data are presented here with the permission of the NCI



induced anti-metastatic effects have also been demonstrated by Maeda et al. (2008) as detailed in the next section on the in vivo effects of lapachol.

Lapachol also displays anti-angiogenic properties, especially when it is coordinated to bismuth (III) (Parrilha et al. 2012). Furanonaphthoquinones are also phytoconstituents of the Bignoniaceae family, and 2-acetylfuranonaphthoquinone (**3**; Table 2) displays higher in vitro antitumor activity than lapachol (Eyong et al. 2008). Compound **3** is available in minute amounts from nature, whereas exposure of lapachol to ozonolysis conditions results in the formation of the expected aldehyde **4** (Table 2) at 70 % yield along with this unusual compound **3** at 30 % yield (Eyong et al. 2008). Pentacyclic derivatives of lapachol such as (±)1,4-naphthoquinones (compound **5** in Table 2) display ten times higher in vitro antitumor activity than lapachol (da Silva et al. 2002). These pentacyclic derivatives can also be considered pterocarpan (**6**; Table 2) derivatives where the A-ring is substituted by the 1,4-naphthoquinone nucleus (da Silva et al. 2002). Pentacyclic 1,4-naphthoquinone derivatives such as **7**–**9** (Salustiano et al. 2010) are active in single micromolar ranges against oxidative stress-resistant K562 and multidrug-resistant (MDR) Lucena-1 human leukemia cells, whereas lapachol **1** and α-lapachol (**10**, Table 2) are not (Salustiano et al. 2010). In addition, these pentacyclic 1,4-naphthoquinone derivatives display low toxicity in lymphocytes activated by phytohemagglutinin, a feature that emphasizes their bioselectivity for cancer cells over normal cells (Salustiano et al. 2010). The cytotoxic effects of these compounds on cells from leukemia patients are related to the activation of apoptosis (Salustiano et al. 2010).

As emphasized by Maia et al. (2011), despite the relevant therapeutic progress obtained with imatinib, clinical resistance to this drug has emerged and reemerged after cytogenetic remission in a group of patients with chronic myeloid leukemia (CML). Maia et al. (2011) have thus evaluated the anti-CML activity and mechanisms of action of LQB-118 (**11**, Table 2), a pterocarpanquinone structurally related to lapachol **1**. LQB-118 treatment resulted in a substantial reduction in viability of two cell lines derived from CML, the vincristine-sensitive K562 cell line and the vincristine-resistant K562-Lucena (a cell line overexpressing P-glycoprotein). These authors observed, in agreement with these results, that the induction of caspase-3 activation by this compound indicated a significant rate of apoptosis, and apoptosis induced by LQB-118 **11** was accompanied by a reduction of P-glycoprotein, survivin, and XIAP expression (Maia et al. 2011).

Although, as stated above, the anti-malarial agent atovaquone was not seen to be an effective antitumor agent, its 2-piperazinyl and 2-piperidinyl analogues have been shown to significantly exert in vitro growth inhibitory effects favourably comparing to the activity of the known cancer chemotherapeutic doxorubicine (Zhou et al. 2009).

In vivo pharmacological and toxicological analyses of the antitumor activity of lapachol

The pharmacokinetic of lapachol in humans has been studied by Niehues et al. (2012a, b). The maximum plasma concentration of this naphthoquinone derivative was seen to be 30 μg/mL. Several reports have demonstrated that lapachol displays in vivo anticancer activity. Indeed, da Consolaçao et al. (1975) showed that the acetylglucosylation of lapachol (**9**, Table 2) resulted in a compound that extended lapachol activity and that was effective against mouse lymphocytic leukemia P-388. These authors reported that mice inoculated with 1 million leukemic cells and treated with the drug for 9 days had an 80 % increase in lifespan compared with control animals (da Consolaçao et al. 1975). Maeda et al. (2008) reported that lapachol can act as a vitamin K antagonist with in vivo anticancer activity. These authors used the B16BL6 mouse metastatic melanoma model and observed that a single oral administration of a highly toxic dose of lapachol (80–100 mg/kg) 6 h before an intravenous injection of tumor cells in the mice dramatically promoted metastasis (Maeda et al. 2008). This increase in metastasis was also observed in T cell-deficient mice and NK-suppressed mice, and in vitro treatment of B16BL6 cells with lapachol promoted metastasis only slightly, indicating that lapachol promotes metastasis primarily by affecting host factors other than T and NK cells (Maeda et al. 2008). The increase in metastasis caused by lapachol was almost completely suppressed by administering vitamin K3 before and 6 h after oral administration of lapachol, and the protein C level was reduced maximally

without an increase in prothrombin time (Maeda et al. 2008). These authors thus suggested that a high dose of lapachol promotes metastasis by inducing a hypercoagulable state as a result of the inhibition of a vitamin K-dependent pathway (Maeda et al. 2008). In contrast, chronic oral administration of low, non-toxic doses of lapachol (5–20 mg/kg) weakly but significantly suppressed metastasis by an unknown mechanism,

Table 2 Illustration of lapachol congeners with in vitro and/or in vivo antitumor activity

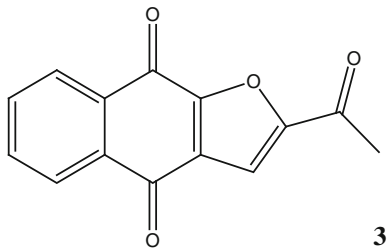
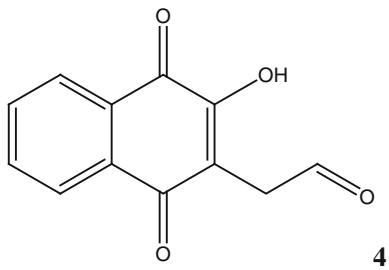
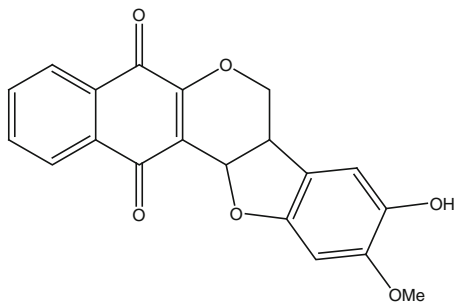
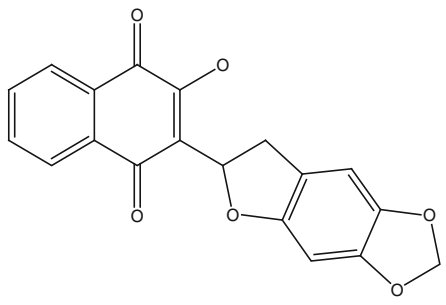
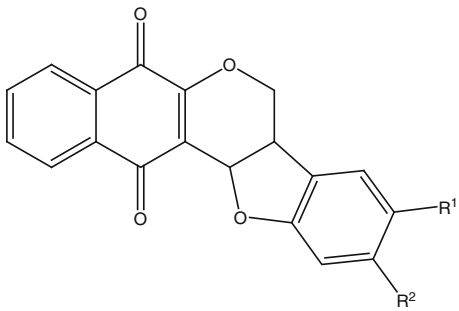
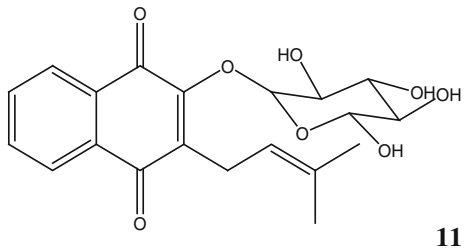
Compounds	Reference
 **3**	Eyong et al. (2008)
 **4**	Eyong et al. (2008)
 **5**	da Silva et al. (2002)
 **6**	Salustiano et al. (2010)

Table 2 continued

Compounds	Reference
 **7** R^1 = OH, R^2 = OCH_3; **8** R^1 = OCH_3, R^2 = OH; **9** R^1 = R^2 = Obn; **10** R^1 = R^2 = H	Salustiano et al. (2010) and Maia et al. (2011)
 **11**	da Consolaçao et al. (1975)

nevertheless suggesting the possible use of lapachol as an anti-metastatic agent (Maeda et al. 2008).

Conclusions

Lapachol is a compound with a relatively simple chemical structure that can be easily derivatized into various subgroups of compounds with increasing levels of anticancer activity both in vitro and in vivo. Lapachol can be obtained by extraction from a large variety of plants; it can also be synthesized in six chemical steps. This compound displays not only antiproliferative activity but also antimetastatic effects, again both in vitro and in vivo. While lapachol has been identified for several decades, it merits further chemical and pharmacological analyses because it has higher antiproliferative and antimigratory effects in cancer cells than in normal cells. Lapachol could therefore lead to the discovery of novel anticancer agents with marked anti-metastatic effects, and the development of such agents is especially important because 90 % of cancer patients currently die from their metastases and not from their primary cancer.

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