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Exploring the Therapeutic Promise of Naphthoquinones: A Spotlight on Lapachol

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Abstract: Medicinal plants possess various biological activities and significantly contribute towards the development of various clinically used medications. In recent years, the research interest in natural drug designs has increased exponentially. Lapachol is a useful phytoconstituent with a quinone ring, reported for its broad-spectrum pharmacological activities, including antimicrobial, anticancer, anti-leishmanial, anti-trypanosomal, molluscicidal, wound-healing, and other activities. The therapeutic values of Lapachol from various plant families have been explored in existing scientific reports, as well as in traditional uses and other potential therapeutic effects. This review highlights updates on the pharmacological activities and other traditional uses of Lapachol.

Keywords: antileishmanial; lapachol; molluscicidal; side effects; traditional.

1. Introduction

The quinone moiety has attracted interest in recent decades due to its diverse pharmacological actions. In 1946, Wendel WB reported that some of the 2-hydroxy-3-alkylnaphthoquinones could inhibit the growth of *Plasmodium*. Quinone compounds generally have a p-bisdienonic ring system in their molecular structure and possess the capacity for reversible chemical reactivity toward oxidation-reduction [1]. Naturally occurring quinones and naphthoquinones are concerned with photosynthesis and are widely distributed in the lower as well as higher species of plants, animals, fungi, etc [2,3].

Lapachol was identified as the most abundant quinone in the family Bignoniaceae and, for the first time, isolated from *T. avellanedae* in 1882 [4]. In Brazil, Lapachol is known as Pau DArc, Ipe-Black, Ipe-purple, and Yellow-Ipe [5]. The blood-brain barrier crossing of lapachol has been demonstrated in various in vivo studies and has been found effective in the treatment of malignant glioma [6]. Lapachol has been traditionally used in Brazil to treat malaria and fever. The antimalarial drug atovaquone, synthetically known as 2-alkyl-3-

hydroxynaphthoquinone, is also an analog of lapachol [7,8]. Other pharmacological activities of Lapachol are listed in Table 1 and diagrammatically represented in Figure 1.

Table 1. Pharmacological activities of Lapachol.

Sr. No.	Disease	Pharmacological activity	References
1	Cancer	Antitumor/anticancer/ antimetastaic activity	[9-15]
2	Chagas' disease	*In vitro* inhibition of amastigotes of *L. viannia* braziliensis and *Trypanosoma cruzi*	[16,17]
3	Disease in fish and mammals	Molluscicidal	[18]
4	Fungal infection	Antifungal	[19]
5	Hepatic cirrhosis	Hepatoprotective	[20]
6	Inflammation	Anti-inflammatory	[21]
7	Leishmania	Antileishmanial	[16-22]
8	Malaria	Antimalarial (*Ae. aegypti*)	[23,24]
9	Microbial infection	Antimicrobial	[25,26]
10	Schistosomiasis	Cercaricidal and schistosomicidal	[27]
11	Ulcer	Antiulcer	[28]
12	Viral disease	Antiviral	[29]
13	Blood clotting	Vitamin K-antagonist antigen	[30]

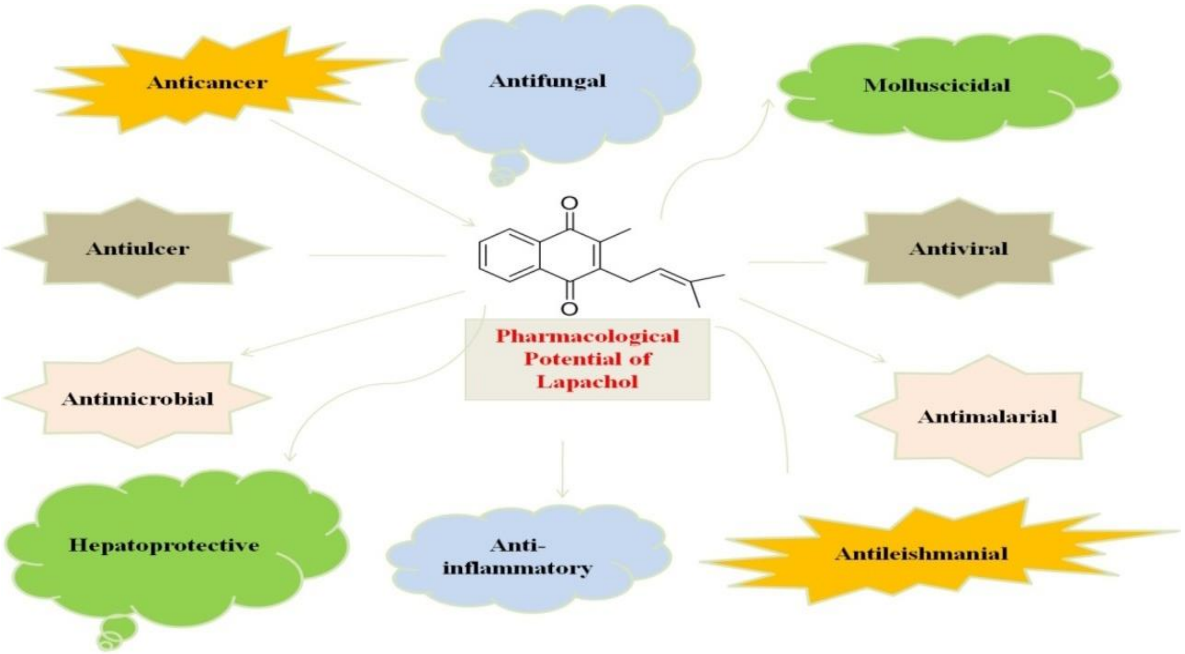

Figure 1. Pharmacological potential of Lapachol.

2. Biological Sources of Lapachol

Lapachol is generally found in bacteria, fungi, and higher plants. Lapachol is mainly distributed in *Bignoniaceae, Verbenaceae, Proteaceae, Leguminosae, Sapotaceae, Scrophulariaceae*, and *Malvaceae* [31]. It is mainly obtained from the plant extract of *T. avellanedae*, Taigu or lapachol wood, Teak wood, and root [32,33]. Some other biological sources of Lapachol are listed in Table 2.

Table 2. Various biological sources of Lapachol.

Sr. No.	Source	Family	Reference
1	*Tabebuia avellanedae*	Bignoniaceae	[32,33]
2	*Penicillium notatum*	Trichocomaceae	[34]
3	*Tectona grandis*	Lamiaceae	[32,35,36]
4	*Tabernaemontana undulata*	Bignoniaceae	[37,38]
5	*Tecoma stans*	Bignoniaceae	[39,40]
6	*Avicennia marina*	Acanthaceae	[41]
7	*Radermachera xylocarpa*	Bignoniaceae	[42]

Sr. No.	Source	Family	Reference
8	*Tabebuia rosea*	Bignoniaceae	[43]
9	*Tabebuia serratifolia*	Bignoniaceae	[43]
10	*Plumbago zeylanica*	Plumbaginaceae	[44]
11	*Kigelia pinnata*	Bignoniaceae	[45]
12	*Aspergillus niger*	Trichocomaceae	[46]
13	*Alternaria alternate*	Pleosporaceae	[46]
14	*Heterophragma adenophyllum*	Bignoniaceae	[47]
15	*Acacia nilotica*	Leguminosae	[48]

3. Chemical Properties

Chemically, Lapachol is 2-hydroxy-3-(3-methylbut-2-enyl)naphthalene-1,4-dione (Figure 2), a yellow color natural pigment, having chemical formula $C_{15}H_{14}O_3$, weakly acidic, low solubility in water and highly soluble in basic solutions [49-51].

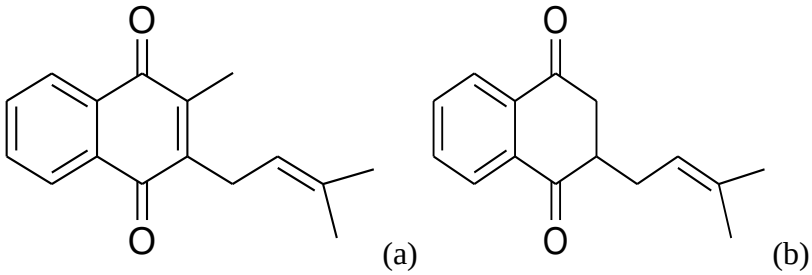

Figure 2. Chemical structures of lapachol (a) and dehydroxylapachol (b).

Various techniques are available for detecting Lapachol in aqueous solutions, blood, urine, and other biological fluids. In 1994, Alcanfor *et al*. determined lapachol in aqueous dispersion using a fluorescent probe 3MPA-CdTe QDs. Lapachol was reduced to the fluorescent product by sodium hydrosulfite, and this method could be used to verify lapachol in serum and pharmaceutical formulations with a limit of detection (LOD) in the g L^{-1} range [52,53]. In 1995, Steinert *et al*. used a combination of HPLC and UV spectrometry for the detection of naphthoquinones in plant extracts, but were unsuccessful in identifying lapachol [54]. In 2004, Fonseca *et al*. recently validated lapachol in lapachone by using absorption detection and isocratic elution at 278 nm with an LOD of 0.3 g L^{-1} in HPLC [55]. In 2013, Aucélio RQ *et al*. utilized the Stern-Volmer Luminescent semiconductor quantum dots (QDs) dispersions model to identify a relationship between the concentration of lapachol and fluorescence. The 3MPA-CdTe QD probe was also shown to be effective for the identification of lapachol in urine samples [56].

4. Potential Pharmacological Activities of Lapachol

Lapachol quinone is present in various plants and fungal species and has been known since ancient times for its antiprotozoal activity against malaria. However, Lapachol shows strong inhibitory activity against leukemic cells, protozoans, and fungal cells.

4.1. Antileishmanial activity of Lapachol.

In 2012, Ali A. determined the anti-leishmanial activity of dichloromethane and *n*-hexane fractions of *T. avellanedae*, and the earlier fraction has higher activity against extra and intracellular *L. major* parasites as compared to the latter one. This fraction of *T. avellanedae* was found to contain lapachol and a mixture of furanonaphthoquinones (5-hydroxy and 8-hydroxy-2-(1'- hydroxyethyl) naphtho[2,3-b]furan-4,9-dione (Figure 3). So, Lapachol might

be responsible for the antileishmanial activity of the plant extract, and the mechanism may involve ROS [57,58].

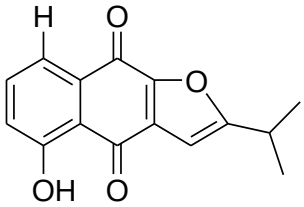

Figure 3. Structure of furanonaphthoquinone.

4.2. Anti-trypanosomal activity of Lapachol.

In 2000, Pinto *et al*. evaluated the biological activities of twenty-two lapachol heterocyclic derivatives against *T. cruzi*. Out of these, the oxazolic and imidazolic derivatives (Figure 4) were found to show 1.5 to 34.8 times superior activity than standard, i.e., crystal violet. These results indicate that these derivatives could be u/'sed as lead molecules for the treatment of Chagas disease [59].

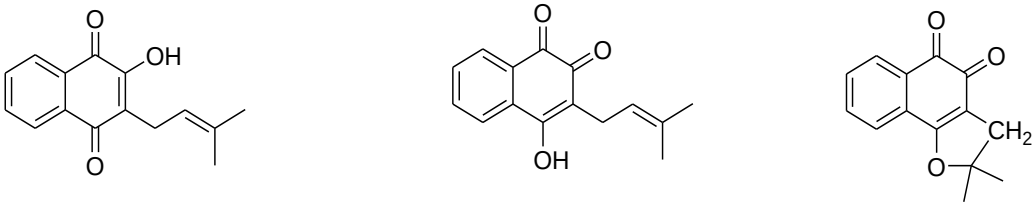

Figure 4. Oxazolic and imidazolic derivatives of lapachol.

In 2002, lapachol derivatives were tested against blood infected with trypomastigote (*T. cruzi*); triacetoxy derivatives were found to have better trypanocidal activity. As lapachol can be readily extracted and its derivatives are readily synthesized, large-scale field tests can be conducted for its applications in large-scale molluscicidal programs [60].

4.3. Antimicrobial activity of Lapachol.

In 2006, Park *et al*. reported the growth-inhibitory activity of Tabebuia impetiginosa (bark) phytoconstituents against Helicobacter pylori (ATCC 43504) using the MIC and paper disc diffusion methods. Standard antibiotics amoxicillin, metronidazole, and tetracycline were used for reference standards. The active components characterized in *Tabebuia impetiginosa* bark extract include anthraquinone-2-carboxylic acid, 2 (hydroxymethyl) anthraquinone, and 2-hydroxy-3-(3 methyl-2-butenyl)-1,4-naphthoquinone (Lapachol). Here, the activity of 1,4-naphthoquinone derivatives (lapachol) against *Helicobacter pylori* was greater than that of metronidazole [61].

Figure 5. Thiosemicarbazone and semicarbazone derivatives of Lapachol.

Moreover, in 2013, Souza *et al*. reported the antimicrobial activity of semicarbazone and thiosemicarbazone derivatives (Figure 5) of lapachol against the bacterial sps. *Staphylococcus aureus*, *Enterococcus faecalis*, and yeast *Cryptococcus gattii*. The thiosemicarbazone derivative of Lapachol was found to be active against eleven clinical isolates of *Paracoccidioides brasiliensis*. The MIC values of thiosemicarbazone derivatives of Lapachol against *S. aureus*, *P. brasiliensis*, *C. gattii*, and *E. faecalis* indicate that these compounds have potential in the development of novel drugs for the treatment of microbial infections [62].

4.4. Antifungal activity of Lapachol.

The antifungal potential of Lapachol is demonstrated in Table 3.

Table 3. Antifungal potential of Lapachol.

S. N.	Source of Lapchol	Fungal strains used for testing	Standard	Mechanism involved	References
1	Species of *Tabebuia*	*C. albicans*, *C. tropicalis* and *Cryptococcus neoformans*	Ketoconazole	Uncoupling oxidative phosphorylation and electron transport inhibition	[63,64]
2	Endophyte extracts of *A. niger* and *A. alternata*	Different pathogenic bacteria and fungi	Bavistin	---------	[65]
3	1,4-naphthoquinone derivatives of Lapachol	*S. aureus*	Vancomycin	----------	[19]

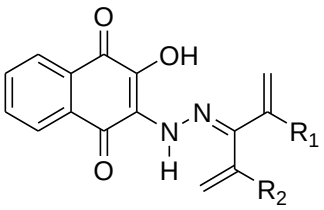

Figure 6. Chemical structure of hydrazine 1,4-naphtoquinone derivatives of Lapachol.

4.5. Molluscicidal activity of Lapachol.

Some studies reported that partially hydrogenated Lapachol derivatives have significantly higher molluscicidal activity than Lapachol itself [18,65]. Sant'Ana A.E.G. *et al*. in 2002 found out the action of Lapachol, its potassium salt, and acetyl derivative against the snail *Biomphalaria glabrata* and its egg masses. The LD_{50} values of Lapachol and its salts indicate a strong molluscicidal activity [60].

4.6. Antiviral activity of Lapachol.

Lapachol's antiviral activities are illustrated in Table 4.

Table 4. Antiviral activity of Lapachol.

S.N.	Lapachol source	Enzyme or viral species against which active	Mechanism	References
1	Lapachol itself	β-Lapachone inhibits eukaryotic DNA-dependent DNA polymerase-α	Redox potential	[66]
2	Lapachol itself	*Herpes virus* hominis types I and II, poliovirus, influenza virus, and vesicular stomatitis virus	--------	[67]
3	1,2-naphthoquinone derivatives	Should be replaced with Lapachol, a 1,4-naphthoquinone compound that has been	Interferon production or	[68]

S.N.	Lapachol source	Enzyme or viral species against which active	Mechanism	References
		demonstrated to inhibit Nsp9 from SARS-CoV-2, which could be an important target in prospecting for ligands with antiviral potential	enzyme inhibition	
4	Lapachol	inhibition of vitamin K epoxide reductase and vitamin K quinone reductase	--------	[69]
5	*Aq.* Extracts of *T. avellanedae* inner bark	Epstein-Barr virus (EBV)	----------	[70]

4.7. Anticancer activity of Lapachol.

Interaction of Lapachol with nucleic acids of the DNA helix leads to inhibition of DNA replication and RNA synthesis, and its interaction with topoisomerase enzymes is known for its anticancer mechanism [31, 71-76]. Molecular modeling studies showed that Lapachol and 2-(1-hydroxyethyl)-naphtho[2,3-b]furan-4,9-dione were active against human estrogen receptor alpha, and this finding could be used in the treatment of breast cancer [77]. Different anticancer studies of Lapachol are shown in Figure 7.

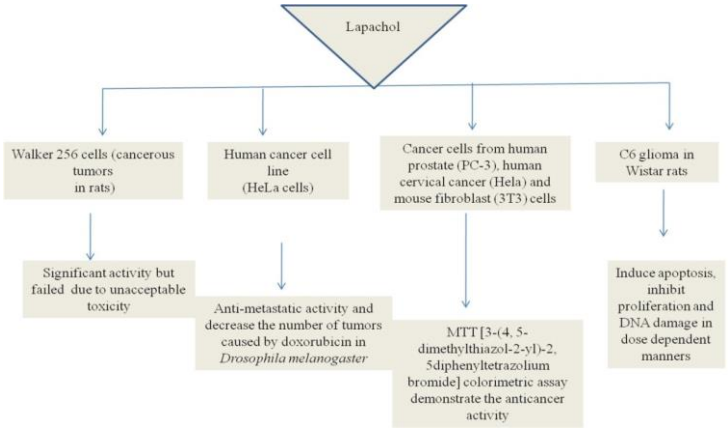

Figure 7. Different anticancer studies of lapachol.

A novel ruthenium(II) complex, along with lapachol, could also induce G2/M phase arrest by downregulating the Aurora-B kinase and downregulating the ROS-mediated apoptosis process in human prostate adenocarcinoma cells [78]. Lapachol's anticancer activity is shown in Table 5.

Table 5. Anticancer activities of lapachol.

S.N.	Source	Type of tumor or cells	Activity	References
1	Lapachol	Walker 256 cells (cancerous tumors in rats)	Significant activity and clinical trials were run by NCI in 1970, but they had to terminate them due to unacceptable levels of toxicity	[11,12]
2	Lapachol	Human cancer cell line (HeLa cells)	Anti-metastatic activity and decrease the number of tumors caused by doxorubicin in *Drosophila melanogaster*	[74]
3	Lapachol (methanolic extract of *Kigelia pinnata* root and its derivative	Cancer cells from human prostate (PC-3), human cervical cancer (HeLa), and mouse fibroblast (3T3) cells	MTT [3-(4, 5-dimethylthiazol-2-yl)-2, 5diphenyltetrazolium bromide] colorimetric assay demonstrate the anticancer activity	[79-81]
4	Lapachol	C6 glioma in Wistar rats	Induce apoptosis, inhibit proliferation, and cause DNA damage in a dose-dependent manner	[82]

4.8. Anti-inflammatory.

Lapachol shows anti-edematogenic activity by carrageenan pedal injection in rats. Initially, carrageenan shows a good anti-inflammatory activity in rats [21, 83-85].

4.9. Wound healing.

Wounds have been treated with natural substances for thousands of years [86, 87]. After isolating lapachol from *Fernandoa adenophylla*, Rauf *et al*. reported the drug's encouraging anti-inflammatory properties [88]. In 2023, Thiago Santos also reported the wound healing properties of Lapachol [89]. The importance of sirtuins in diabetic wound healing was illustrated by Bibi *et al*. in 2021, who identified a novel possible sirtuin activator, lapachol [90]. Lapachol may have inhibited extracellular matrix hyperplasia during wound healing and potentially reduced the development of hypertrophic scar, according to research by Matsui *et al* [91].

In 2010, Sharma *et al*. reported the wound-healing activity of the aqueous extract of *K. pinnata* by the excision wound model. Aqueous extract of the bark of *K. pinnata* was found to contain a high amount of free ferulic acid, Lapachol, stigmasterol, and β-sitosterol, which implies that β-sitosterol may be responsible for the epithelization activity due to the free radical scavenging action [92]

4.10. Toxicity.

Orally administered lapachol also produced toxic effects in animals, with oral LD50 values of 0.621 g/kg and 2.4 g/kg in BALB/c mice and albino rats, respectively. Symbols of toxicity in dogs and monkeys include moderate to severe anemia, normoblastosis, reticulocytosis, elevated serum alkaline phosphatase activity, leukocytosis, and prothrombin times [93]. Some research results also indicate that Lapachol is not toxic to mothers, although it leads to fetal growth retardation and does not interfere with embryonic development, as well as the pre-implantation period. However, when administered during the organogenic period at the same dose level, it induced high fetal death incidences [94].

4.11. Snake bite.

Lapachol and synthetic derivatives were evaluated *in vitro* and *in vivo* against snake venoms of *Bothrops*. Natural quinone and other related synthetic quinones showed antivenom activity and reduced the inflammatory effects produced by venom. This pharmacological activity could be used in snakebite venom research and improve the management of cases of venomous snakebites [95-97].

5. Conclusion

As the currently available drugs are associated with various adverse effects, the current global attention to traditional medicine has led to rapid growth in the remedies used by various ethnic groups worldwide. The present article highlights the pharmacological potential of Lapachol, including antimicrobial, anticancer, antileishmanial, antitrypanosomal, molluscicidal, and wound-healing activities. So, Lapachol has the potential for further evaluation in animals and humans.

Author Contributions

Writing – review & editing, A. L., N. J., T. H., S. K., V. K., M. K. G., and N. A. All authors have read and agreed to the published version of the manuscript

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Conflicts of Interest

The authors declare no conflict of interest.

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