

A Review on Evaluation of Pharma Profile of Lapachol of Tectona Grandis

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ABSTRACT: Tectona grandis(common name Teak, Tamil-Tekku, Bengali-Segun) is known for it's timber value, renowned dimention stability, extreme durability, hard, resists decay and insect from olden time. Accumulation of certain quinone derivatives mainly responsible for these qualities.Tabebuia impetiginos a,also known as "ipe" (Pau d'asco) along with Tectona grandis,Tabebuia avellanadae, species of plants tested for active chemical substance naphthoquinone also known as lapachol a natural quinone first isolated by Paterno in 1882 from Brazilian cerrado.Development of new drug specially to treat cancer between 1983 to 1994 were derived from natural sources [1] [2]. Lapachol is also found in verbenaceae, proteaceac, leguminoseae,sapotaceae,scrophulariaceae and Malvaceae and the first two natural analogues of lapachol to be isolated were b lapachone and alpha-lapachone.

KEYWORDS: lapachol,Napthoquinone, reactive oxygen species, DNA scission

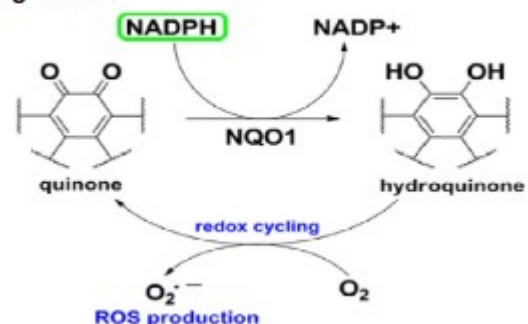
I. INTRODUCTION

Tectona grandis Linn(TG) is commonly known as "teak" of family verbenaceae,large deciduous tree of 30-35 metre tall (**Figure 1**) with light brown bark,leaves simple,opposite,broadly elliptical or acute or acuminate,with minute granular dots,flowers are white in colour,small and have a plesant smell [3].The plant TG is probably the most widely cultivated high value hardwood(HVW) in the world and it's native to India,Mayanmar and south-East Asian countries. It is now one of the most important species of tropical plantation forestry.The various phytoconstituents isolated from Tectona grandis are Juglone, which has been reported to have antimicrobial activity[4], betulin aldehyde shows anti-tumor activity [5] and lapachol also revealed anti-ulcerogenic activity[6]. Quinone are classified by the aromatic moieties present in this structure and the napthoquinone constitutes the naphtalenic ring [7]. Ortho and para-quinoid based cytotoxins have their ability to generate semiquinone radicals by bioreduction ,which then accelerate intracellular hypoxic profile.Two essential mechanisms are linked to the effect of (**Figure 2**)



Figure 1: Aerial parts of *T. grandis* Linn.

Figure:2



Napthoquinone such as oxidative stress and nucleophilic alkynyation (Bolton et al.,2000)[8],which induce the so called "reactive oxygen species" that can cause damage to cells. Lapachol proved to be a vitamin-k antagonist antigen,thus possibly targeting vitamin-k dependent reactions [9],besides also being bioactivated by P450 reductase to reactive species which promotes DNA scission,through redox cycling with generation of free radicals [10].Recently new series of compounds via molecular hybridization of napthoquinones (such as naturally occuring lapachol) with pterocarpan (naturally occuring iso flavonoids) was designed and synthesized.

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II. SYSTEMATIC POSITION

Kingdom: Plantae - Plants
Subkingdom: Tracheobionta - (Vascular Plant)
Superdivision: Spermatophyta - 9Seed Plants)
Division: Magnoliophyta - (Flowering Plants)
Class: Magnoliopsida - (Dicotyledons)
Subclass: Astridae
Order: Lamiales
Family: Verbenaceae - Verbena family
Genus: Tectona L.f. - Tectona
Species: Tectona grandis L.f. –Teak

III. OCCURANCE

Lapachone is one of most versatile compounds found in Bignoniaceae Verbenaceae, Proteaceae, Leguminoceae and other different families illustrated below.

Occurrence of lapachol in families and species

Family :Bignoniaceae

Species :

Tabebuia flavescens DC.	Stereospermum tetragonum
T. guayacan Hemsl.	Stereospermumpersonatum
T. avellaneda Lor. ex Griseb.	Catalpa longissima
T. serratifolia (Vahl.) Nichols	Cybistax antisiphilitica
T. rosa	Macfadyena unguis-cati
T. bata (E. Mey) Sandw	Meloea quadrivalvis
T. pentaphylla (Linn) Hemsl.	Newbouldia laevis
T. heptaphylla	Family:Verbenaceae
Haplophragma adenophyllum fil	Species : Tectona grandis L.
Heterophragma adenophyllum	Avicennia tomentosa Jacq
Kigelia pinnata	Avicennia officinalis
Phyllarthron comorense	Family:Proteaceae
Radermachera sinica Br.	Species : C. teretifolium R.
Paratecoma peroba (Record) Kuhl	
Family:Leguminosae	
Tecoma araliaceae DC	Species: Diphysa robinoide
Bent	

Family :Bignoniaceae

Species : T. undulata

Stereospermum suaveolens DC.

S. kunthianum

Zeyhera digitalis

tiliaceus

Z. tuberculosa

Millingtonia hortensis Linn

kawakamii

Family:Sapotaceae

Species :Bassia latifolia

Family:Malvaceae

Species :Hibiscus

Family:Scrophulariaceae

Species :aulownia

Traditional Usage of Tectona grandis Leaves: are cooling, haemostatic, depurative, anti-inflammatory and vulnerary. They are useful in treating against inflammations, leprosy, skin diseases, pruritus, stomatitis, indolent ulcers, haemorrhages and haemoptysis.

IV. DIFFERENT PHARMACOLOGICAL PROFILE OF LAPACHOL OF TECTONA GRANDIS

Anti-metastatic activity

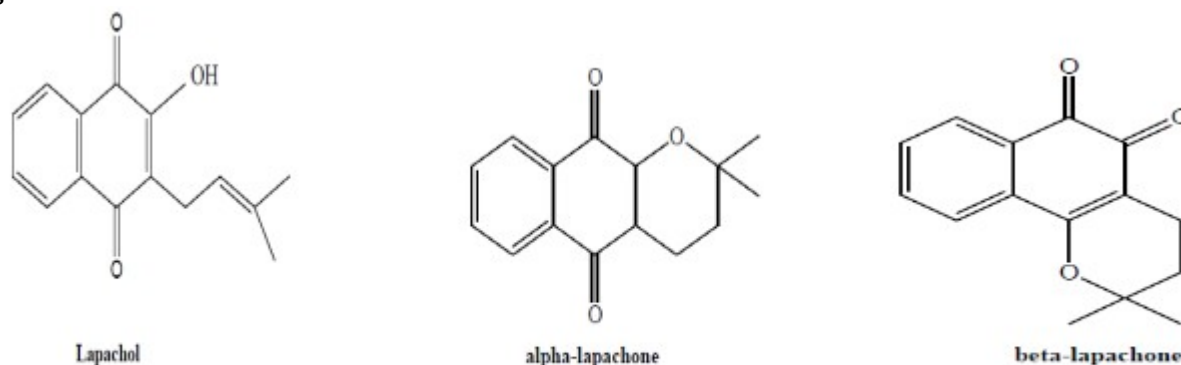
Metastasis is the major process responsible for the death in cancer patients [11]. The literature reveals that the lapachol a naphthaquinone isolated from *Tectona grandis* effects on a human cancer cell line and evaluated the potential of as an anti-metastatic in vivo assay. Accordingly the lapachol, in the maximal non-toxic concentration on HeLa cells of 400 µg/ml (corresponding to 1012 molecules of the drug/cell), induce alterations in the protein profile and inhibit cellular invasiveness, thus representing an important anti-metastatic effect [12].

Antitumor Activity

Lapachol isolated from *Tectona grandis* demonstrated highly significant activity against cancerous tumors in rats [13]. Its antitumor property alone and in combination with radiation was evaluated in female Swiss albino mice, 6-8 weeks old, bearing sarcoma-180 (S-180) ascetic tumor cells. In female mice 2×10^5 , S-180 viable ascetic cells were injected intraperitoneally. These ascetic bearing mice were treated with different concentrations of lapachol (50, 100 mg/kg body weight) at various days along with radiation (CO 60 gamma radiation 3, 6 Gy). In another group of ascetic bearing animals, the animals were irradiated with 3, 6 Gy of gamma radiation in combination with 50, 100 mg/kg body weight of lapachol. Therapeutic cure ratio (T/C) and percentage change in body weight were taken as parameters for the assessment of antitumor activity. There was increase in the T/C ratio in the animals treated with lapachol or irradiated with gamma radiation. However, there was highly significant increase in the T/C ratio in the group of animals treated with lapachol in combination with radiation. The change in the T/C ratio was concentration and dose dependent. There was significant change in the percentage of body weight [14]. Despite the lack of significant toxicity even in large oral dose levels, sufficiently high blood levels were not attained to show a therapeutic effect. [15] It led to the termination of further clinical development of lapachol. Because of its antitumor activity, it is an ideal candidate for systematic modification to develop an understanding of its structure-activity relationships and thus eventually to develop analogs with improved activity.

In a 1968 study, lapachol demonstrated highly significant activity against cancerous tumors in rats. The antitumor activity of lapachol was tested against carcinoma 755, leukemia L-1210, P-1534 leukemia, Sarcoma 180 and Walker 256 carcinosarcoma. Of these, only Walker 256 showed sensitivity to lapachol when administered daily as intraperitoneal injection at levels up to those producing limiting toxicity. The activity of lapachol against the Walker 256 intramuscular tumor system was first noted when the compound was administered by the same route. Its antitumor effect was then studied in detail through dosage of implanted animals by a number of parenteral routes and orally and by a variety route on treatment regimens [18]. Because of the highly significant activity in the Walker 256 intramuscular tumor system, especially when the drug is given twice daily by the oral route, and because of the relatively mild signs of general toxicity, lapachol was approved by the Cancer Chemotherapy National Service Center (CCNSC) for human clinical trials [18].

However, in 1974, the National Cancer Institute (NCI) [19] concluded that the high concentrations required for efficient chemotherapy in human cancer treatment, unfortunately also gave rise to extremely toxic side-effects, thereby justifying its rejection [20][21].

Figure :- 3

In a small study in 1980 with nine patients with various cancers (liver, kidney, breast, prostate and cervix), pure lapachol demonstrated an ability to shrink tumors and reduce feeling of pain caused by these tumors and achieved complete

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remissions in three of the patients. It is believed that the antitumor activity of lapachol may be related to its interaction with nucleic acids. Additionally it has been proposed that interaction of the naphthoquinone moiety between base pairs of the DNA helix occurs with subsequent inhibition of DNA replication and RNA synthesis [22].

Studies conducted by Kumagai et al.,[10], Kumagai and Shimojo [23] demonstrated that oxidative stress induced by lapachol occurs in response to the P450 reductase enzyme, causing changes in the DNA. Lapachol itself does not have a direct effect on DNA, however when it interacts with the Cytochromes P450 the effect on DNA can be observed. Lapachol has also been demonstrated to reduce the number of tumors caused by doxorubicin in animal model heterozygous for the tumor suppressor gene [24]. The frequency of reduction of tumors was directly proportional to the concentration of lapachol. At a concentration of 20 mg/mL, there was a reduction of 64% in the frequency of tumors induced by DXR. At a concentration of 40 mg/mL, the reduction was 71% and at a concentration of 60 mg/mL a 76% reduction was noted. There was tumor reduction throughout the experimentation, concentrated primarily on the certain part of the body.

AntiUlcer Activity

Lapachol, a naphthaquinone isolated from the roots of *Tectona grandis* given at a dose of 5 mg/ kg twice daily for 3 days was found to have an anti-ulcerogenic effect on subsequently induced experimental gastric and duodenal ulcers in rats and guinea-pigs. Its action appears to be associated with an effect on the protein content of gastric juice, and it reversed aspirin-induced changes in peptic activity, protein and sialic acid[6].

Cytotoxic potential

Different extract of teak checked against HEK293 and CEF cell line and showed high toxicity at lowest concentration. Against CEF cells, chloroform extract of bark showed 87% inhibition at 10ug/ml concentration with methanol extract of wood (61%) and hexane extract of leaf (54%) showed. Chloroform extract of bark was able to exhibited high toxicity (95.3 %) against HEK293 cells line. Methanol extracts of wood (76.6 %) and bark (73.2 %) were next in position showing toxicity against the latter. Supported to this report of [47] presence of lapachol, dehydro-alpha-lapachone, betulinic acid etc with reported toxicity and has been reported in teak [26,27]. In bioassay investigation in brine shrimp lethality test with petrol extract of *T. grandis* root heartwood exhibit a good level of activity where lapachol was found active at LC50 of 5 ppm [28].

Antimicrobial and antifungal profile

Lapachol, like many naphthoquinones, interferes with the electron transport system and inhibits the cell respiratory mechanism. In a study pursued in the 1940's, found that lapachol at a concentration of 100 mg/ml, inhibits the uptake of oxygen in *Plasmodium knowlesi* by 74 % and the succinate oxidase system by 26 %. These findings lead to the conclusion that lapachol has antimalarial activity against *Plasmodium falciparum* via respiratory mode. However, the exact mechanism of action remains controversial. It is hypothesized that lapachol either inhibits the interaction between the cytochromes b and c or directly inhibits an unknown enzyme between the two cytochromes [29]. It was also found that lapachol has activity against *Helicobacter pylori*, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacillus* and *Clostridium* species with an MIC ranging from 1.56 to 25 mcg/ml. Besides, it was reported that lapachol has a significant effect against *Candida albicans*, *Candida tropicalis*, and *Cryptococcus neoformans*, that was similar to Amphotericin B. The presumed antifungal activity of lapachol is believed to be due to its interaction with the cellular membrane [30-32]. As part of systematic search for new bioactive lead structures from African medicinal plants, lapachol has been isolated from *Newbouldia laevis* and demonstrated antiplasmodial activity as well as antimicrobial activity against some Gram positive and Gram negative microorganisms [33,35]. Recently Breger et al. [36] identified the antifungal role of lapachol against *Candida elegans* and its pathogenicity.

Antiviral activity

Lapachol was found to be effective against certain viral strains including herpes virus types I and II. Naphthoquinones have been documented to show effectiveness against four strains of the flu, polio and vesicular stomatitis virus. Lapachol and its enamine showed larvicidal and insecticidal activity against *Artemia salina* and *Aedes aegypti*, respectively and in terms of cytotoxicity against A549 human breast cancer cells [37].

The mechanism of action of these quinones is supposed to be via DNA and RNA polymerase and retrovirus reverse transcriptase inhibition. Furthermore, β -lapachone is presumed to interfere with the replication of the HIV-1 virus via transcriptase inhibition [38]. It is reported that lapachol decreases the replication of viruses in human subjects but as yet there is no clinical evidence [38].

Anti-inflammatory activity

T. avellanedae is believed to have an inhibitory effect on the histamine releasing cells which consequently leads to anti-inflammatory effects. Lapachol, in the preliminary study produced a significant anti-inflammatory action in rats [39].

According to another in vitro study, lapachol and its analogs were shown to have antipsoriatic effects by inhibiting the growth of human keratinocyte cell line HaCaT and reducing inflammations. The authors of the study[40] concluded that lapachol has similar antipsoriatic activity to that of anthralin in inducing damage to the cell membranes of the keratinocyte. However, the authors did not report the degree of similarity or difference between the two agents [40].

Anti angiogenic activity

Neovascularization is an essential process in tumor development, it is conceivable that anti-angiogenic treatment may block tumor growth. In angiogenesis, nitric oxide (NO) is an important factor which mediates vascular endothelial cell growth and migration. Whether beta-lapachone can induce endothelial cell death or has an anti-angiogenic effect is still an enigma. Investigation of the in vitro effect of beta-lapachone on endothelial cells, including human vascular endothelial cell line, EAhy926, and human umbilical vascular endothelial cells (HUVEC). Results revealed that (a) the intracellular cGMP levels and the mitochondria membrane potential (MMP) decreased, and calpain and caspases were activated, during beta-lapachone-induced endothelial cell death; (b) co-treatment with calpain inhibitors (ALLM or ALLN) or the intracellular calcium chelator, BAPTA, but not the general caspase inhibitor, zVAD-fmk, provided significant protection against apoptosis by preventing the beta-lapachone-induced MMP decrease and cytoplasmic calcium increase; (c) addition of NO downregulated the beta-lapachone-induced cGMP depletion and protected the cells from apoptosis by blocking the MMP decrease and the calcium increase; and (d) exogenous NO protects endothelial cells against the cell death induced by beta-lapachone, but not the anti-angiogenic effect. From the data above, it is demonstrated that NO can attenuate the apoptotic effect of beta-lapachone on human endothelial cells and suggest that beta-lapachone may have the potential for anti-angiogenic activity.

Anti parasitic activity:Lapachol has been used as a topical barrier to trematodes specifically on blood fluke, the *Schistosoma mansoni*, which causes schistosomiasis. This parasite lives in water and enters the host by penetration through the skin. This pathogen can cause a complicated disease, which can sometimes be fatal. It has also been stated that oral lapachol formulation is effective against skin penetration. In addition, lapachol is claimed to have some effect against *Trypanosoma cruzi*, which causes trypanosomiasis or Chaga's disease and the disease can be present in either acute or chronic form and has no known cure to date [29]. However, there is no documented data available in either humans or animal models. Schmeda-Hirschmann [41] reported the antiparasitic activity of lapachol and related naphthoquinones.

Leishmanicidal activity :Teixeira et al.,[42] reported that lapachol exhibits marked leishmanicidal activity in vitro. Recently, Lima et al. [36,43] also reported the antileishmanial activity of lapachol and its derivatives. The mechanism by which lapachol induces lysis of intracellular amastigotes in vitro is not yet clear. However, a characteristic of the naphthoquinones (especially lapachol and β -lapachone) is that they interfere with the oxygen metabolism of the tumour cell, blocking cell respiration and generating free oxygen radicals. Besides free oxygen radicals, there is evidence that nitric oxide (NO) production, which follows the induction of nitric oxide synthetase by IFN- γ , plays an important role for the death of intracellular amastigotes in murine macrophages. NO is considered the most important metabolite involved in *Leishmania* killing in mice [42].

Molluscicidal activity :Lapachol was assayed for molluscicidal activity against *Biomphalaria glabrata* and showed significant molluscicidal activity.[44] The naphthoquinone is bioactivated by P 450 reductase into reactive species which in turn promote DNA scission through the generation of superoxide anion radicals by redox cycling. Silva et al., [45] and Santana et al.,[46] synthesized derivatives of lapachol for a molluscicidal assay. The partially hydrogenated lapachol derivative, obtained from the catalytic reduction of lapachol, showed molluscicidal activity significantly higher than that of lapachol itself. These findings confirm the importance of lapachol as a pivotal starting material for the production of biologically active compounds [45].

Anti Proliferative Activity: β -lapachone exerts its anti-proliferative action in cultured human prostate carcinoma DU145 cells. Exposure of DU145 cells to β -lapachone resulted in growth inhibition and induction of apoptosis in a dose-dependent manner as measured by MTT assay, fluorescent microscopy, and flow-cytometry analysis. The increase in apoptosis was associated with a dose-dependent up-regulation in pro-apoptotic Bax expression, down-regulation of anti-apoptotic Bcl-2, and proteolytic activation of caspase-3 protease. It was found that β -lapachone decreased the levels of cyclooxygenase (COX)-2 mRNA and protein expression without significant changes in the levels of COX-1, which was correlated with a decrease in prostaglandin E2 (PGE2) synthesis. Furthermore, β -lapachone treatment markedly inhibited the activity of telomerase in a dose-dependent mode. Additionally, the expression of human telomerase reverse transcriptase (hTERT), a main determinant of the telomerase enzymatic activity, was progressively down-regulated by β -lapachone treatment. Taken together, these findings provide important new insights into the possible molecular mechanisms of the anti-cancer activity of β -lapachone.

V. CONCLUSION

Tectona grandis, is a medicinal plant with versatile nature, apart from possessing high value of hardwood timber, it is also the unique source of various types of compounds having diverse chemical structure. Although in 1974 the National Cancer Institute have ruled out the possibility of the use of lapachol specially in fighting cancer, due to its high toxicity, this quinone and its derivatives still remain promising drugs for cancer treatment. The pharmacological activities of lapachol and its natural derivatives, like antimetastasis, anti abscess, anticancer, anti ulcer, which is reviewed in this paper, can be used as a future research endeavors.

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