

# Therapeutic Potential of *Pterocarpus santalinus* L.: An Update

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## ABSTRACT

Recently there has been increasing interest in plants and plant-derived compounds as raw food and medicinal agents. In Ayurveda, an Indian system of traditional medicine, a wide spectrum of medicinal properties of *Pterocarpus santalinus* is described. Many important bioactive phytochemicals have been extracted and identified from the heartwood of *P. santalinus*. Bioactive compounds typically occur in small amounts and have more subtle effects than nutrients. These bioactive compounds influence cellular activities that modify the risk of disease rather than prevent deficiency diseases. A wide array of biological activities and potential health benefits of *P. santalinus* have been reported, including antioxidative, antidiabetic, antimicrobial, anticancer, and anti-inflammatory properties, and protective effects on the liver, gastric mucosa, and nervous system. All these protective effects were attributed to bioactive compounds present in *P. santalinus*. The major bioactive compounds present in the heartwood of *P. santalinus* are santalin A and B, savinin, calocedrin, pterolinus K and L, and pterostilbenes. The bioactive compounds have potentially important health benefits: These compounds can act as antioxidants, enzyme inhibitors and inducers, inhibitors of receptor activities, and inducers and inhibitors of gene expression, among other actions. The present review aims to understand the pharmacological effects of *P. santalinus* on health and disease with "up-to-date" discussion.

**Key words:** Antioxidant activity, oxidative stress, phytochemicals, *Pterocarpus santalinus*

## INTRODUCTION

Plants as natural products are a valuable source of bioactive compounds and have been used for medicinal purposes in all over the world. Recently, scientific attention to oriental medicine has increased in context of the discovery of novel drugs for treating various diseases including cancer and diabetes.<sup>[1,2]</sup> The World Health Organization (WHO) endorses the evaluation of the potential benefits of plants as effective therapeutic agents, especially in areas where there is a lack of safe modern drugs.<sup>[3]</sup> One-third of total drugs (35%) in the USA and 80% of drugs used in fast-developing countries such as China and India are derivatives of phytoextracts.<sup>[4,5]</sup> India has a rich heritage of medicinal plants of wide diversity, which are used by the local population and traditional healers for the treatment of several diseases. One such plant is *Pterocarpus santalinus*, which is widely used for the treatment of various ailments due to its extensive medicinal properties.

*P. santalinus* is a small-to-medium-sized deciduous tree belonging to the Fabaceae family. It is widely distributed in the tropical regions of the world, especially in India, Sri Lanka, Taiwan, and China.<sup>[6]</sup> Earlier reviews explored the phytochemistry, pharmacology, and ethnomedicinal values of *P. santalinus*.<sup>[7,8]</sup> Bioactive compounds present in the plant's heartwood have been shown to have a wide range of biological activities,

suggesting the potential of *P. santalinus* for the treatment of various diseases.<sup>[7,9]</sup> *In vitro* and *in vivo* studies showed that the heartwood and bark have exhibited antidiabetic, antimicrobial, anti-inflammatory, and hepatoprotective activities [Figure 1].<sup>[9-11]</sup> In Ayurveda, an Indian system of traditional medicine, it is mentioned that the heartwood of the plant is used as external application for treating inflammation, diabetes, headache, skin diseases, and jaundice, and in wound-healing.<sup>[12,13]</sup> This review summarizes the current literature on the compositional profile and pharmacological activities of important phytochemicals present in the heartwood and various extracts of the plant.

## Bioactive compounds present in heartwood of *P. santalinus*

Phytochemical analysis of the plant showed the presence of carbohydrates, flavonoids, terpenoids, phenolic compounds, alkaloids, saponins, tannins, and glycosides.<sup>[11,14]</sup> In addition, the available literature demonstrated the presence of several specific components in heartwood powder—in particular, pterocarpol; santalin A, B, and Y; pterocarptriol; isoptercarpalone; pterocarpodiolones with  $\beta$ -eudesmol; cryptomeridiol,<sup>[15]</sup> several nonspecific compounds such as isoflavones; isoflavonoid glucosides; triterpenes; sesquiterpenes, and related phenolic compounds such as  $\beta$ -sitosterol; lupeol; epicatechin; lignans; and pterostilbenes [Figure 2 and Table 1].<sup>[16-21]</sup> Pterostilbene, a structural analog of resveratrol, is more stable than resveratrol. Pterostilbene (3,5-dimethoxy-4'-hydroxy-trans-stilbene) isolated from the heartwood

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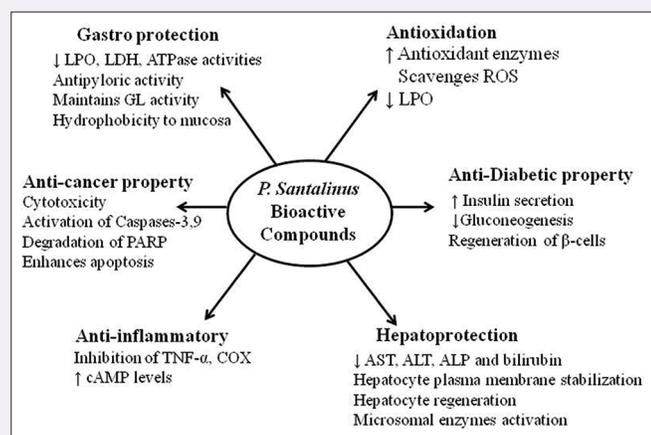


Figure 1: Schematic representation of potential benefits of *P. santalinus*

showed anti-inflammatory, antioxidant, and anticancer properties.<sup>[22,23]</sup> Nonflavonoid polyphenols contain different subgroup compounds such as simple phenols, benzoic acids, hydrolysable tannins, cinnamic acid, acetophenones, phenylacetic acid, lignans, coumarins, benzophenones, xanthenes, and stilbenes.<sup>[24]</sup> Thirty naturally occurring phenolic acids, in particular hydroxyl and polyhydroxybenzoic acids, have been reported to have biological activities, among them 3-hydroxybenzoic acid, gentisic acid, α and β resorcylic acid, and vanillic acid.<sup>[25]</sup> In addition, aurone glycosides OH-1 methyl-3',4',5'-trimethoxy aurone, 4'-O-rhamnoside, 6,4'-dihydroxy aurone, 4'-O neohesperidoside and isoflavone glycoside, 4',5'-dihydroxy-7-methylisoflavone, and 3-O-beta-D-glucoside are also present in *P. santalinus*.<sup>[16,17]</sup> Six closely related sesquiterpenes isolated from the heartwood of *P. santalinus* using different solvents such as petroleum, benzene, and chloroform are isoptercarpalone, pterocarpatriol, pterocarpdiolone, and the known β-eudesmol, pterocarpol, and cryptomeridiol.<sup>[15,16]</sup> Dehydromelanoxin-6, melanoxin-7, melanoxoin-14, S-30-hydroxy-4, 40-dimethoxydalbergione-15, and melannein-16 were the known compounds present in heartwood of *P. santalinus* and identified with the comparison of nuclear magnetic resonance and mass spectrometry data of the established literature.<sup>[26]</sup>

Stilbenes represent a small class of secondary plant metabolites derived from the phenylpropanoid pathway. Stilbenes are phenolic compounds displaying two aromatic rings linked by an ethane bridge, structurally characterized by the presence of a 1,2-diarylethene nucleus with hydroxyls substituted on the aromatic rings.<sup>[27]</sup> One specific stilbene, namely, pterostilbene was reported in *P. santalinus* heartwood.<sup>[23,28]</sup> Pterostilbene, a methyl ether of resveratrol, has recently attracted much attention, as a growing number of reports describe promising pharmacological properties such as anti-inflammatory, antioxidant, and anticancer properties.<sup>[29]</sup> Lignan compounds can be divided into several different types, such as the dibenzyl butyrolactones (arctigenin and savinin), furofurans (pinoresinol and eudesmin), and dibenzylbutanes (secoisolaricresinol).<sup>[30]</sup> Lignans are *cis*-o-hydroxycinnamic acid and are dimers (2 C6-C3 units) resulting from tail-tail linkage of 2 coniferyl or sinapyl alcohol units.<sup>[31]</sup> Specific lignans, namely, savinin, calocedrin, and eudesmin were reported in the heartwood extract of *P. santalinus*.<sup>[20]</sup> Wu *et al.*, isolated two bioactive components from heartwood of *P. santalinus*, namely one new phenanthrenedione compound pterolinus K and another new chalcone compound pterolinus L [Figure 3], which acted as lead compounds for the development of anti-inflammatory agents.<sup>[32]</sup> Studies also showed

Table 1: Class of phytochemicals and related compounds present in heartwood of *P. santalinus*

Class of compounds	Compounds present in heartwood
Aurone glycosides	6-hydroxy 5-methyl 3,4,5-trimethoxy aurone, 4-O-α-L- rhamnopyranoside, 6,4-dihydroxy aurone, 4-O-rutinoside <sup>[21]</sup>
Benzofurans	Pterolinuses A-E <sup>[26]</sup>
Chalcone	Pterolinus L <sup>[31]</sup>
Hydroxybenzoic acid	Parahydroxybenzoic acid, <sup>[25]</sup> gentisic acid, α-resorcylic acid, β-resorcylic acid, vanillic acid
Isoflavone glycoside	4,5'-dihydroxy-7-methylisoflavone, <sup>[17]</sup> 3-O-beta-D-glucoside
Lignans	Savinin, calocedrin <sup>[20]</sup>
Neoflavonoids	Pterolinuses F-J, melanoxin, <sup>[26]</sup> melanoxoin, S-3-hydroxy-4,4-dimethoxydalbergione melanin
Phenanthrenedione	Pterolinus K <sup>[31]</sup>
Santalins	Santalin A, B, and Y <sup>[21]</sup>
Sesquiterpenes	Isoptercarpalone, pterocarpatriol, pterocarpdiolone, β-eudesmol <sup>[16]</sup> pterocarpol, cryptomeridiol
Sterols	β-sitosterol <sup>[21]</sup>
Stilbene	Pterostilbene <sup>[28]</sup>
Triterpenes	Acetyloleanolic aldehyde, acetyloleanolic acid, lupeol <sup>[16]</sup>

that *P. santalinus* heartwood contains ferric ion (Fe<sup>3+</sup>), Ni<sup>2+</sup>, and Ba<sup>2+</sup> elements.<sup>[33]</sup> The bark ethanolic extract of *P. santalinus* also showed the presence of aspartic acid, glutamic acid, alanine, serine, glycine, threonine, lysine, asparagine, histidine, arginine, cystine, glutamine, proline, phenylalanine, and leucine amino acids.<sup>[34]</sup>

## In vitro studies

### Radical-scavenging and antioxidant activity

Free radicals are electrically charged molecules, and an excessive generation of free radicals is linked to many human diseases. Reactive oxygen species (ROS) including hydroxyl radicals cause oxidation of lipids, proteins, and DNA; damage the structure and function of cells; and lead to the development of diseases. Animal studies have shown that dietary phytochemical antioxidants are capable of removing free radicals. Among them, phenolic and polyphenolic compounds, such as flavonoids in edible plants, exhibit potent antioxidant activities.<sup>[29]</sup> The free radical-scavenging activity of extracts of the leaves of *P. santalinus* has been evaluated using *in vitro* studies. The methanolic extract of the leaves exhibited radical-scavenging activity for 1,1-diphenyl-2-picrylhydrazyl (DPPH), nitric oxide, and hydrogen peroxide.<sup>[13,35]</sup> Studies by Kumar demonstrated Fe<sup>3+</sup>-reducing capacity and DPPH radical-scavenging activity in the methanolic extract of heartwood. The reductive capabilities and scavenging activity were found to increase with increasing concentrations and were compared with butylated hydroxyanisole (BHA).<sup>[36]</sup> Reports also revealed that pterostilbene exhibited strong *in vitro* antioxidant activity against free radicals such as DPPH, 2,2'-azino bis (3-ethylbenzothiazoline-6-sulfonate) (ABTS), hydroxyl, superoxide, and hydrogen peroxide.<sup>[37]</sup> Very limited reports are available related to the scavenging activities of extracts isolated by using different solvents and isolated active compounds. Further elaborate and confirmative studies using the heartwood of *P. santalinus* are needed.

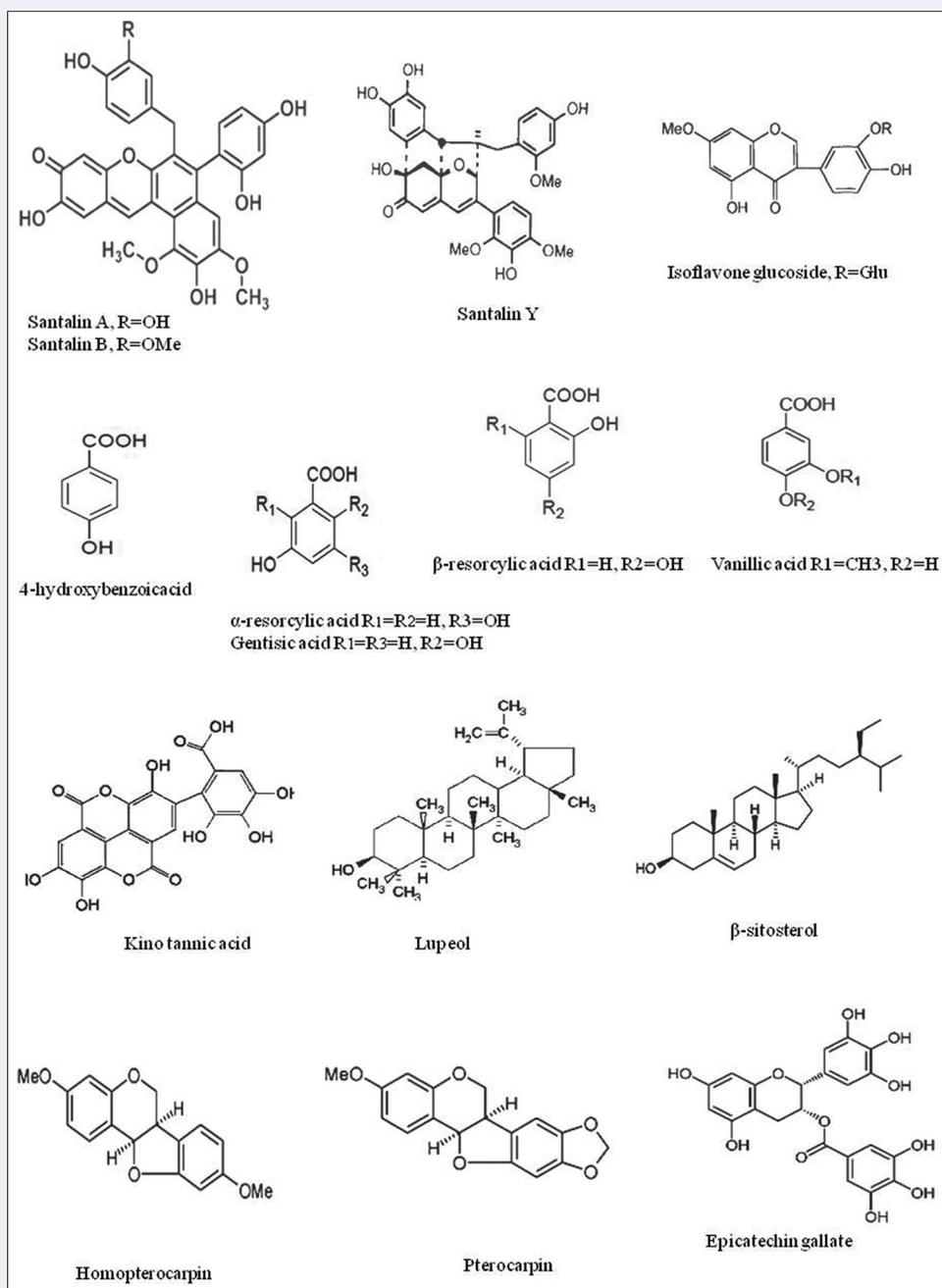


Figure 2: Phytocompounds present in *P. santalinus* heartwood

### Antibacterial activity

Infectious diseases are a major cause of global morbidity and mortality. They account for roughly 50% of all deaths in tropical countries.<sup>[38]</sup> Chemical and synthetic drugs that are used to treat microbial infections are associated with multiple side effects. Human pathogens have developed drug resistance after the routine human consumption of these drugs, and it is a big challenge for researchers to develop safe and effective medication for the treatment of infectious diseases. Several research groups have studied the antibacterial and radical-scavenging activities of plant extracts, and they proved that the extracts showed effective antibacterial and radical-scavenging activities with no side effects.<sup>[39,40]</sup> The antibacterial activity of leaf and bark extract of *P. santalinus* was

tested against Gram-positive bacteria such as *Staphylococcus aureus* ATCC 25933, *Staphylococcus epidermidis* MTCC 3615, *Bacillus subtilis* MTCC4 41, *Enterococcus faecalis* ATCC2912, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853. The bark extract has shown greater inhibition activity than the leaf extract.<sup>[35,41]</sup> The antibacterial activities of 21 timber-yielding plants were tested against uropathogenic bacteria, and *P. santalinus* was among the most inhibitory-activity-exhibiting plants.<sup>[42]</sup> A comparative study was done to find out the antibacterial activities of the methanol and aqueous leaf extracts of *P. santalinus*. The methanolic extract has shown greater inhibitory activity than the aqueous extract.<sup>[43]</sup> Silver nanoparticles prepared from the leaf extract of *P. santalinus* exhibited antibacterial potential against Gram-positive and Gram-negative strains.<sup>[44]</sup> Other

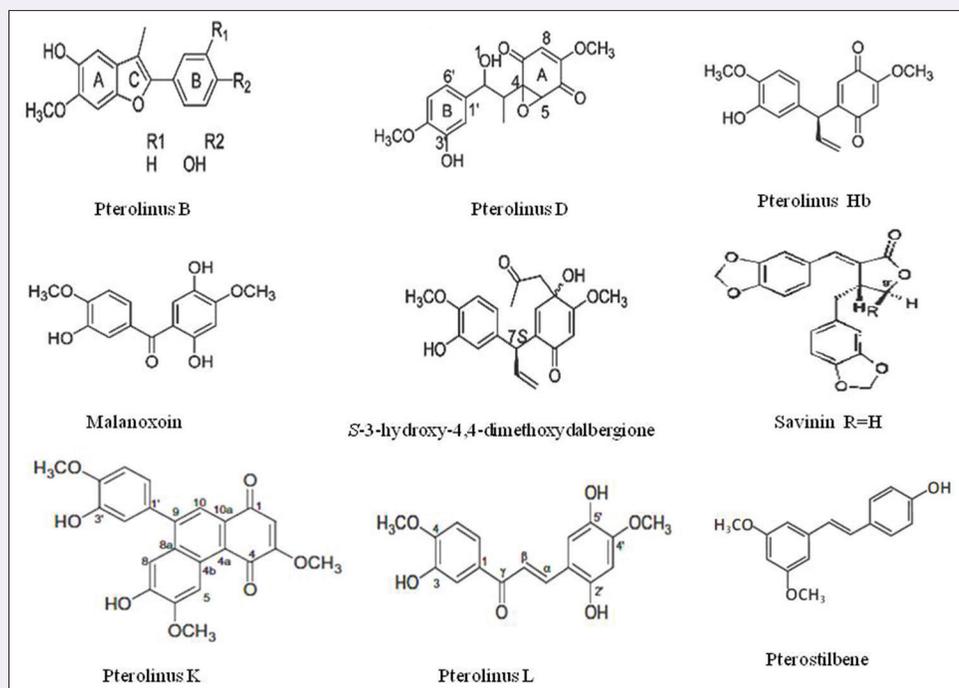


Figure 3: Phytocompounds present in *P. santalinus* heartwood showing cytotoxic activity against cancer cells

reports also have shown that lignans present in *P. santalinus* could have antibacterial properties.<sup>[45]</sup> Its anti-*Helicobacter pylori* effect was tested by culturing *H. pylori* on gastric epithelial cells in the presence/absence of *P. santalinus* extract. A reduction in the activity of urease, normal appearance of gastric epithelial cells under electron microscopic examination, and decrease in lipid peroxidation (LPO) and lactate dehydrogenase (LDH) activities suggested an antipyloric effect.<sup>[46]</sup> *In vitro* antimicrobial activities of heartwood extracts need confirmation against various pathological microbes and standardization in that context.

## In vivo studies

### Anti-inflammatory effect

Inflammation plays a crucial role in the initiation and progression of pathological conditions. The majority of phytomedicines exhibit therapeutic efficacy by exerting anti-inflammation and cytotoxic activities. It is well known that T lymphocytes enhance chronic inflammatory conditions by activating the inflammatory cells, such as mast cells, eosinophils, neutrophils, and macrophages, resulting in massive production of chemical mediators and pro-inflammatory cytokines.<sup>[20,47]</sup> The anti-inflammatory activities of lignan compounds isolated from the heartwood of *P. santalinus* have been studied in RAW264.7 cells and splenocytes. Tumor necrosis factor (TNF)- $\alpha$  is one of the pro-inflammatory cytokines secreted in chronic inflammatory and allergic diseases. TNF- $\alpha$  production in lipopolysaccharide-stimulated RAW264.7 cells was inhibited at a dose of 25  $\mu\text{g}/\text{mL}$  by savinin, a lignan compound. The molecular mechanism of inhibitory action of the compound is due to its structural similarity with that of a butyrolactone ring and its polarity on the C-9 position.<sup>[20]</sup> Specific lignans, namely, savinin, calocedrin, and eudesmin were reported in the heartwood extract of *P. santalinus*. These compounds were found to inhibit TNF- $\alpha$  and also showed antiproliferative effect with an  $\text{IC}_{50}$  value at 40  $\mu\text{g}/\text{mL}$ .<sup>[10]</sup> Studies by Kumar have shown significant inhibitory activity

of the heartwood extract (500  $\mu\text{g}/\text{mL}$ ) against carrageenan-induced inflammation in paw edema.<sup>[37]</sup> Five new benzofurans, six neoflavonoids, and pterolinus isolated from heartwood, including pterolinus B, showed potent anti-inflammatory activity with an  $\text{IC}_{50}$  value at 0.19  $\mu\text{g}/\text{mL}$ .<sup>[26]</sup> Phenanthrenedione (pterolinus K) and chalcone (pterolinus L) compounds isolated from the heartwood of *P. santalinus* showed notable inhibition of superoxide anion generation and elastase release by human neutrophils in response to formyl-L-methionyl-L-leucyl-L-phenylalanine (FMLP)/cytochalasin B (CB) with  $\text{IC}_{50}$  values at 0.99  $\mu\text{M}$  and 0.94  $\mu\text{M}$ , respectively.<sup>[32]</sup> However, other biological activities and anti-inflammatory mechanism(s) exhibited by lignans and savinins require further studies.

### Effect on diabetes

Traditionally made heartwood cups for drinking water have been used as a treatment for diabetes.<sup>[48,49]</sup> Diabetes mellitus (DM) is a metabolic syndrome that consists of ineffective insulin regulation leading to derangements in carbohydrate metabolism.<sup>[50]</sup> Rao *et al.* found that the ethanolic fraction of *P. santalinus* showed hypoglycemic activity at a dose of 0.25 g/kg body weight/day.<sup>[51]</sup> The active fraction of ethylacetate: methanol (9:1) of bark ethanolic extract has shown antihyperglycemic activity at a dose of 150 mg/kg body weight by improving insulin secretion and alterations in the carbohydrate metabolism.<sup>[11,52]</sup> Coadministration (250 mg/kg body weight) of heartwood aqueous extract along with vitamin E to streptozotocin-induced diabetic rats caused significant lowering of blood sugar at a dose of 250 mg/kg body weight/day.<sup>[3]</sup> The molecular mechanisms involved in the treatment of diabetes by individual as well as whole extracts of either the bark or heartwood of *P. santalinus* need to be thoroughly investigated. Several researchers paid much attention in studying the effects of *P. santalinus* against diabetes using classical methods. However, future studies are required to explore the antidiabetic activity using isolated bioactive compounds at the molecular level.

### Effect on cancer

Natural phenolic compounds act on multiple targets in pathways and mechanisms related to carcinogenesis, tumor cell proliferation and death, inflammation, metastatic spread, angiogenesis, and radiation resistance. Chemoprevention with food phytochemicals is meanwhile regarded as one of the most important strategies for cancer control. Phenolic compounds from medicinal herbs include phenolic acids, flavonoids, stilbenes, lignans, and others.<sup>[53]</sup> Bioactive compounds isolated from *P. santalinus* exhibit cytotoxic and anticancer properties. Treatment of cervical adenocarcinoma HeLa cells with a methanolic extract of *P. santalinus* resulted in growth inhibition and induction of apoptosis with the IC<sub>50</sub> value 40 µg/mL. The methanolic extract of *P. santalinus* induced apoptosis through the mitochondrial pathway involving cytochrome-c release from mitochondria, the activation of caspase-9 and caspase-3, and degradation of peroxisome-activated receptor protein (PARP).<sup>[10]</sup> Benzofuran compounds isolated from heartwood showed cytotoxicity against Ca9-22 cancer cells with an IC<sub>50</sub> value 0.46 µg/mL.<sup>[26]</sup> The inhibitory activity of savinin on T cell proliferation was the highest from the methylene chloride extract (25 µg/mL) in comparison with the other solvents ethyl acetate, n-butanol, and water.<sup>[10]</sup> The therapeutic efficacy of pterostilbene was tested against breast cancer, lung cancer, colon cancer, prostate cancer, and pancreatic cancer.<sup>[54]</sup> Pterolinus K and pterolinus L isolated from heartwood have shown significant anticancer property with IC<sub>50</sub> values at 10.86 µM, 9.81 µM, and 17–8.2 µM, against cancer cell lines HepG2, Hep3B, and A549, respectively.<sup>[32]</sup> Future studies are required that apply isolated compounds against various cancers and essential signalling pathways involved in the pathogenesis.

### Hepatoprotective mechanisms

The use of natural remedies for the treatment of liver diseases has a long history, beginning with Ayurvedic treatment and spreading to the Chinese, European, and other systems of traditional medicine. The pharmacological validation of each hepatoprotective plant should include evaluation of its efficacy against liver diseases induced by various agents.<sup>[55]</sup> *P. santalinus* bark and heartwood are rich in flavonoids and protect the liver against chemical-induced toxicity. Studies showed that aqueous (45 mg/mL) and ethanol (30 mg/mL) bark extracts of *P. santalinus* restored CCl<sub>4</sub>-induced liver damage in rats.<sup>[9]</sup> The therapeutic efficacy of heartwood extract was tested against D-galactosamine-induced liver damage in albino rats by administering at a dose of 400 mg/kg body weight/day.<sup>[6]</sup> *In silico* docking studies revealed that potent compounds pterocarpol and cryptomeridiol, present in *P. santalinus* heartwood, targeted the HBx proteins of hepatitis B virus, and were thus reported as strong drug candidates.<sup>[56]</sup> Itoh *et al.* reported that *P. santalinus* suppresses hepatic fibrosis in chronic liver injury.<sup>[57,58]</sup> Though it has many medicinal properties against various ailments, it has never been tested against alcohol-induced hepatotoxicity. In addition, researchers must elucidate the underlying protective molecular mechanisms of isolated compounds against liver-related diseases.

### Gastroprotective mechanisms

Gastric mucosal injury results as a consequence of various conditions and activities, including alcohol intake, refluxed bile salts, stress, aging, *H. pylori* infection, and most of the nonsteroidal anti-inflammatory drugs. The ethanol extract of *P. santalinus* was evaluated for gastroprotection against ibuprofen-induced ulcers in albino rats. The extract (150 mg/kg body weight/day) showed a significant reduction in gastric lesions, increase in activities of antioxidant enzymes, and decrease in membrane-bound adenylypyrophosphatase (ATPase) activities, and the ability to maintain the functional integrity of cell membranes.<sup>[14]</sup> The ethanolic extract of heartwood restored the activities of tricarboxylic

acid cycle (TCA) enzymes, prevented mitochondrial dysfunction by providing mitochondrial membrane integrity including a hydrophobic nature to the gastric mucosa, and reversed the damage caused by ulcerogens at a dose of 200 mg/kg body weight/day.<sup>[59]</sup> The plant extract's ability against various chemical agents that disturb the gut microbial flora, which would be useful in physiology and also protect the intestinal mucosa, has not been studied.

### Hypolipidemic activity

Generally, phenolic phytochemicals exhibit antioxidative and hypolipidemic activities and thereby protect the liver and heart against a wide variety of pathological conditions, including hyperlipidemia, by inhibiting lipid synthesis.<sup>[60]</sup> Modification of lipids is an integral part of the initiation and progression of atherosclerosis, in part by its effects on lipid profile. Circulatory very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) are considered to be powerful markers and risk factors for cardiovascular disease (CVD). The lipid-lowering activity of the bark extract (150 mg/kg body weight/day) was studied in diabetic rats.<sup>[11]</sup> Reduction in total cholesterol and lipoproteins and increase in high-density lipoprotein-cholesterol (HDL-C) was observed in diabetic rats treated with an aqueous extract of heartwood (250 mg/kg body weight/day) in combination with vitamin E.<sup>[3]</sup> A chloroform extract of heartwood (400 mg/kg body weight/day) significantly lowered the serum total cholesterol and triglycerides in D-galactosamine-intoxicated rats.<sup>[6]</sup> Pterostilbene has also been reported to have hypolipidemic properties comparable to clinically used fibrate lipid-lowering drugs.<sup>[61]</sup> Daniel *et al.* reported that pterostilbene increased LDL and reduced blood pressure in hypercholesterolemic human volunteers.<sup>[62]</sup> The main etiologic factor in atherogenesis is oxidation of LDL. Reports showed that the 3-hydroxybenzoic acid, gentisic acid, α- and β-resorcylic acid, and vanillic acid present in heartwood of *P. santalinus* have potential inhibitory properties against LDL oxidation.<sup>[24]</sup> A plant extract is a source of numerous complex compounds not tested against protein factors, which can regulate the expression of various transcription factors involved in enhanced lipid synthesis.<sup>[63]</sup>

### Angiogenesis and wound-healing activity

The process of generating new blood vessels from preexisting ones is called angiogenesis. The process of angiogenesis is controlled by positive and negative regulators. Chorioallantoic membrane (CAM) assay is one of the most well-established and commonly used *in vitro* models for evaluating angiogenesis and vasculogenesis. Jadhav *et al.* demonstrated that an acetone extract of *P. santalinus* (1 mg/mL) stimulated angiogenesis more significantly than alcohol and benzene extracts. The CAM angiogenic effect was mediated by the proliferation of endothelial cells without any toxicity.<sup>[63]</sup> Oral administration (2 g/kg or 1 g/kg body weight) and intraperitoneal injection (500 mg/kg body weight or 1 g/kg body weight) was made to study the toxicity of the heartwood extract in rat models.<sup>[64]</sup> The plant also has a wound-healing property, and this was demonstrated by Biswas *et al.* in normal and diabetic wound rat models, and concluded that the ointment made from the plant is effective in treating acute wounds.<sup>[64]</sup> The angiogenic activity of the plant may be attributed to the phytoconstituents present in the extract. The wound-healing property represents the biochemical and biomechanical properties of the plant. Although the biological activities of specific compounds were not established and it is suggested that bioactive compounds present in the extract might act by stimulating growth factors or signal cascade systems, further confirmative studies are needed.

### Other pharmacological uses

The heartwood extract showed strong analgesic action in mice by inhibiting acetic acid-induced writhing by increasing the latency period.<sup>[37]</sup> Phenolic acids, in particular hydroxyl and polyhydroxybenzoic acids, 3-hydroxybenzoic acid, gentisic acid,  $\alpha$ - and  $\beta$ -resorcylic acid, and vanillic acid present in the heartwood of *P. santalinus* have been reported to have antifungal, antimutagenic, anti-inflammatory,<sup>[24]</sup> and nematocidal activity,<sup>[65]</sup> and a thyroid peroxidase inhibitor effect.<sup>[66]</sup> Many other reports also have shown that lignans possess antiviral, antiallostatic, and antimutagenic properties.<sup>[33,45,67]</sup> Aurone glycosides isolated from heartwood have been reported to exhibit leishmanicidal activity against *Leishmania donovani*, *Leishmania enrietti*, and *Leishmania major*.<sup>[68]</sup> Additionally, it has been reported to inhibit *in vitro* erythrocytic stages of *Plasmodium falciparum* strains.<sup>[69]</sup> The Indian traditional medicinal system, Ayurveda, suggested that *P. santalinus* could be used to treat various medical complications such as hemorrhage, dysentery, eye diseases, and mental aberrations, and to act as an aphrodisiac and diaphoretic.<sup>[70]</sup> It is used in treating leprosy, bone fracture, scorpion sting, hiccup, and snakebite.<sup>[13]</sup> *P. santalinus* is highly valued for its heavy, dark claret-red sanders, which yields 16% of the red coloring matter santalin, used as a coloring agent in pharmaceutical preparations and foodstuff.<sup>[7]</sup>

### Perspectives on future research

From the compositional point of view, the phytochemicals present in the heartwood of *P. santalinus* are very complex compounds. Many compounds that were identified are general preliminary compounds, but each preliminary compound is a mixture of many more compounds, which are not as yet identified as therapeutic agents. Further research is necessary to provide a detailed characterization of the compounds present in the preliminary compounds. Limited studies have suggested the radical-scavenging and beneficial effects of the heartwood of *P. santalinus*, and the molecular biological mechanisms of the biological activities and physiological effects need further study; the bioavailability and metabolism of the compounds have not been reported. Further studies on these aspects would provide useful data for substantiating the physiological effects of these compounds. A limited area of research has explored this plant as a therapeutic agent, and there is a need to extend studies against a wide variety of pathological conditions. Most of the biological activities and physiological effects of the plant extracts have been studied *in vitro* or in animal models. Clinical and human intervention studies are very limited; therefore the biological and physiological effects of the isolated compounds of the heartwood are also worth investigation.

## CONCLUSIONS

*P. santalinus* has significant hepatoprotective, antioxidant, antimicrobial, and anti-inflammatory activities. The phytochemicals present in *P. santalinus* also showed antidiabetic, hypolipidemic, anticancer, gastroprotective, and wound-healing properties. The therapeutic properties of phytochemicals present in *P. santalinus* extract appear to have a concerted mode of action and conferred protection against various disease complications. Finally, the current review provides the evidence to enable other researchers to use *P. santalinus* as an efficacious natural drug. Further preclinical and clinical studies for adequate evaluation of the safety and therapeutic efficacy of *P. santalinus* are recommended.

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### Conflicts of interest

There are no conflicts of interest.

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