Article

Caesalpinia sappan
A medicinal and dye yielding plant

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Abstract

Natural products have provided a variety of lead structures, which serve as templates for the development of new drugs. The water kept in ***Caesalpinia sappan* Linn.** (*Sappan lignum*) heartwood is being used in Kerala as herbal drinking water for its antithirst, blood purifying, antidiabetic, improvement of complexion and several other properties. The plant is also being used worldwide for a large number of traditional medicinal purposes. Modern day research confirms its cytotoxic, antitumor, antimicrobial, antiviral, immunostimulant and several other activities. Several triterpenoids, flavonoids, oxygen heterocycles, etc. were isolated. Brazilin is found to be the main constituent of the plant responsible for several of its biological activities. The use of heartwood as a colouring agent for wine, meat, fabric, etc. is well established. It has the potential to hit the market as a safe natural colouring agent with good medicinal value for food products, beverages and pharmaceuticals. There is also a scope for further research to establish its medicinal properties and to identify lead compounds for drug development.

Keywords: *Caesalpinia sappan,* sappan wood, heartwood, colouring agent, brazilin, traditional medicines, ayurvedic formulations, chemical constituents, plant drugs.

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Introduction

Back to nature is not merely a slogan. The last forty years have seen a resurgence of interest among researchers in seeking new medicinal agents from plants. This can be attributed to the fact that synthetic and presently available medicines are either too expensive or tend to bring out side effects. In addition, there are many diseases still requiring antidotes. As a result of modern isolation techniques and pharmacological testing procedures, new plant drugs usually find their way in to medicines as purified substances.

***Caesalpinia* Linn.** (Family: *Caesalpiniaceae*) species are being used traditionally and have a wide variety of medicinal properties. ***Caesalpinia sappan* Linn.** is one among them, commonly known as Brazil or Sappan Wood and *Bakam* or *Patang* in Hindi. The tree is cultivated in the gardens for its large, ornamental panicals of yellow flowers. Its branches, when interlaced, make a strong barrier. It is propagated from seed and is quick growing. It is a spreading tree or shrub up to 10 m in height, found wild and as an escape in South India, West Bengal, Orissa and Madhya Pradesh, Malaya and Sri Lanka and cultivated throughout the Asian tropics. The wood is orange red, hard, very heavy, straight grained with a fine and even texture. Branches, rufous-pubescent armed with small prickles. Leaves large hairy to glabrous, bearing small prickles at the base; pinnae 9-14 pairs; leaflets subsessile, oblong, membranous, obliquely truncate, 10-20 pairs per pinna. Flowers yellow in panicle. Pods green, 3-4 seeded and beaked. Seeds ellipsoid and black[1-3].

The heartwood of the plant is widely used in traditional medicine. Chemical investigation resulted in the isolation of novel and interesting phytochemicals possessing potent biological properties. Due to its vast and proven medicinal properties and use as dyeing agent, the wood has received both domestic and international market and being exported to USA and Europe from India, Philippines and from several other countries. The present review discusses the dyeing properties, traditional uses, pharmacological and other activities and reported chemical constituents of various

parts of the plant with special reference to heartwood.

Dyeing properties

Plant dyes were the dominant materials used for textile dyeing in Ancient China, Japan, India and many other countries. Sappan wood was one of the most widely used plant dye for its red colour. It was exported from South East Asia to Europe as dried wood chips. The red wood obtained from this species is similar to the wood obtained from ***Caesalpinia echinata*** **Lam.** which is endemic to the Atlantic Coastal Forest. Both are known as Brazil or Brasil wood in trade and yield same dyestuff. By manipulating the *p*H of the dye bath by the addition of wood ash water or vinegar, the dyers' produce everything from deep egg plant to lavender and maroon to ox-blood red colour. The mordanted dye with alum displays good fastness towards washing[4].

The dye is reported to have anti-inflammatory activity. The pigment find use in manufacture of facials which are resistant to light heat and water and are non-irritating[3] .

The wood was formerly used in calico printing of cotton, wool and silk and later on, largely replaced by synthetic dyes. The heartwood is being used to colour wines and meat. The roots of the plant called 'Yellow wood' are also used to make yellow dye.

Traditional medicinal uses

There are innumerable references of the use of this wood in the traditional medicine. The plant is one of the ingredients of an indigenous drug 'Lukol'™ which is administered orally for the treatment of non-specific leucorrhoea (post IUD) and gave encouraging results in stopping bleeding following IUD insertions[3]. The wood is a component of 'Vicco Vajradanti'™, a famous tooth paste and tooth powder of India. The powerful astringent, haemostatic, healing properties of the wood helps to stop bleeding in gums and give firmness and strength to the gums and hence, it is useful in mobile teeth, aphthous ulcers, stomatitis and gum erosions because of its strong healing action. It is also commonly used in several other Ayurvedic formulations (Table 1).

According to Ayurveda, the heartwood is bitter, astringent, sweet, acrid, refrigerant, vulnerary, depurative, constipating, sedative and haemostatic. It is useful in vitiated conditions of *pitta*, burning sensation, wounds, ulcers, leprosy, skin diseases, diarrhoea, dysentery, epilepsy, convulsions, menorrhagia, leucorrhoea, diabetes, haemoptysis, haemorrhages, stomatopathy and odontopathy[1-3]. As per Yunani system, the wood is very bitter, stops bleeding from the chest and lungs, heals wounds, ulcers, improves complexion and useful in rheumatism.

The decoction of the wood is a powerful emmenogogue being used in India, Brazil, China and several other countries. In China and Malaysia, it is used for disturbances of menstrual functions. The heartwood is reputed to have blood-vitalizing activity and used in the treatment of toxic side effects resulting from radiation and chemotherapy in traditional Chinese medicine. In Malaysia it is used as antimalarial and in Philippines as anti-anaemic. In South Korea it is considered as an abortifacient. It has been used as a haemostatic, analgesic, anti-inflammatory agent and as a medical treatment for confusion and thrombosis in traditional Oriental medicine[5]. Sappan leaves are a component of *Jamu*, a traditional herbal medicine in Java.

The small core of heartwood produces a dark red solution in water and is being used as herbal drinking water in Kerala, since time immemorial for its antithirst, blood purifying, antidiabetic, complexion enhancer and several other properties.

Caesalpinia sappan

Table 1 : List of sappan wood containing Ayurvedic formulations and their uses

S. No.	Formulations	Uses
1. Asavams and Arishtams		
1.	Useerasavam	Astringent, alterative and tonic. Useful in diarrhoea, intestinal and pulmonary haemorrhagia.
2.	Chandanasavam	Diuretic and urinary antiseptic. Used in gonorrhoea, spermatorrhoea and other urinary diseases.
3.	Dasamoolarishtam	Bitter tonic, alterative and stimulant. Useful in cough, meno-nervous diseases, anaemia, jaundice, piles and as a prenatal tonic. Used to increase vigour, sperm count and physical health. Also used in gas troubles, hiccup, cough, vomiting, tuberculosis, lack of appetite, dropsy, etc.
4.	Mritasanjeevani Sura	Rejuvenator, ideal Ayurvedic tonic for vigour and vitality.
5.	Saribadyasavam	Alterative, cooling and tonic. Used in diabetes, skin diseases, scrofula, rheumatic pain, syphilis, etc.
2. Ghritams		
1.	Kalyanaka ghritam and Mahakalyanaka ghritam	Used in psychosis, epilepsy, poisoning, loss of memory and for body nourishment.
2.	Dasaswarasa ghritam	Used for the troubles of *pitta*.
3.	Sarvamayanthaka ghritam	Good for most of the diseases. About 80 diseases due to *vata*, 40 diseases due to *pitta* and 20 diseases due to *kapha* can be cured.
4.	Brihachagaladi ghritam	Good for *vata*, epilepsy and tuberculosis.
3. Kashayams		
1.	Drakshadi kashayam	Good for intestinal disturbances, irritation of the extremities, vertigo, psychosis, etc.
2.	Mahatiktakam kashayam	All diseases related to *pitta*, viz. leprosy, scabies, intestinal disturbances, thirst and vertigo. Useful in syphilis.
4. Thailams		
1.	Triphaladi thailam	Useful in eye and ear diseases.
2.	Irimedadi thailam	Antiseptic, deodorant, mild rubefacient, astringent and analgesic. Indicated in pyorrhoea, bleeding of gums, gingivitis, toothache and other dental diseases.
3.	Bala thailam	Used externally for the conditions of *vata*.

Pharmacological activities

The reported pharmacological properties of heartwood and various other parts are summarized in Table 2.

Cytotoxic and antitumor properties

Various extracts of dried aerial parts exhibited strong cytotoxic properties when tested *in vitro* on several cancerous cell lines. The water and methanol extracts exhibited low IC_{50} values indicating the potent activity against LEUK-U 937, SNU 1, LEUK-HL 60, multi-drug resistant CA-KB-VI, MT-4, HE-1, CA-9 KB, CA-JTC-26 and several other cancerous cell lines. The inhibitory concentrations of DNA topoisomerase-1 against water and methanol extracts were found to be 100 mg/ml and 400 mg/ml, respectively indicating the potent cytotoxic effect of the water extract[6-11]. The methanol, 50% methanol and water extracts of heartwood showed antiproliferative activities against human HT-1080 fibrosarcoma cells[12]. Aqueous extracts of wood exhibited cytotoxic activity against hepatocellular carcinoma cell lines, Hep3B and HepG2[13]. These results are confirmed by the *in vivo* experiments. Ethanol (50%) extract of dried stem showed antitumor activity in LEUL-P388 cell treated mice at 200 mg/kg body weight i.p.[14] The water extract of the wood and its protein fractions also exhibited antitumor properties against sarcoma 180 (ascites) treated mice given intraperitoneally[15-16].

Antimicrobial activity

The essential oil obtained from the leaves and 95% ethanol and water extracts of the wood showed strong

antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Salmonella typhosa* and *Escherichia coli*[10, 17, 18]. The essential oil exhibited antibacterial activity against *Salmonella paratyphi, Staphylococcus albus, Streptococcus viridans*[17] and the 95% ethanol extract against *Mycobacterium smegmatis*[18] and *Shigella dysenteriae*[10]. The plant extract also exhibited antimicrobial activity against *Staphylococcus, Diplococcus, Corynebacterium, Shigella baydii* and several other species. The leaf oil also possesses antifungal activity against *Aspergillus nidulans, A. niger, A. oryzae, Curvularia lunata* and *Candida albicans*[17]. A saponin obtained from the plant exhibited strong antimicrobial activity against *Bacillus subtilis, Aspergillus niger, A. flavus, Salmonella stanley* and *Proteus vulgaris*[19]. These studies confirm the wide use of the plant for antidysenteric, wound healing, lumbago and vulnerary purposes.

Antiviral activity

The hot water extract of dried bark of the plant exhibited antiviral activity. The extract showed the activity against Herpes simplex-1, measels, polio virus-1 and Hepatitis virus in *in vitro* studies[20, 21]. It also showed antiviral activity *in vivo* against Herpes simplex-1 infected mice at 5mg/animal dose[20]. Among 300 plants tested, ***C. sappan*** is one of the ten herbs/plants identified as effective for its anti-HbsAg (Hepatitis B surface antigen) capability[22].

Anti-inflammatory activity

The methanol extract of the heartwood showed anti-inflammatory activity[23]. Among the 130 herbal medicines tested for inhibition of hyaluronidase activity ***C. sappan*** is one of the six active plants, with the methanol extract at 5 mg/ml concentration showing more than 50% inhibition of hyaluronidase activity[24]. Hematein isolated from heartwood had been in use in Oriental medicine both as an analgesic and an anti-inflammatory agent. A recent study showed that after eight weeks of treatment with hematein (0.05% in diet), the extent of atherosclerotic lesions were significantly reduced without change in plasma lipoprotein levels, but probably related to the inhibition of vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemotactic protein-1 (MCP-1) expression resulting in an amelioration of lesion development in rabbit[25].

Table 2 : Reported pharmacological properties of Sappan

S. No.	Pharmacological property	Part used	Extract	References
1.	Anti-anaphylactic	Heartwood	Water	42, 44
2.	Antibacterial	Leaves, Heartwood	Essential Oil, Ethanol & Water	10, 17, 18
3.	Anticoagulant	Heartwood	Water	41
4.	Anticomplementary	Heartwood	Several extracts	30
5.	Antifungal	Leaves	Essential Oil	17
6.	Anti-inflammatory	Heartwood	Methanol	23
7.	Antitumor	Stem, Heartwood	Ethanol, Water, Protein Fraction	14-16
8.	Antiviral	Bark, Heartwood	Water	20, 21
9.	Barbiturate potentiation	Heartwood	Methanol	38
10.	Cytotoxic	Aerial parts, Dried bark, Heartwood	Water, Methanol, Ethyl acetate	6-11
11.	Enzyme stimulation			
	i. Glutamate pyruvate transaminase	Heartwood	Water	32
	ii. Tyrosinase	Heartwood	Ethanol	36
12.	Enzyme inhibition	Stem	Chloroform,	34, 35
	i. Phosphodiesterase		Water	
13.	Immuno stimulant	Heartwood	Protein fraction	15
14.	Semen coagulation	Stem, Heartwood	Ethanol	14

Immunostimulant properties

The protein fraction of the wood increased the peritoneal cells when given i.p. to mice indicating the immunostimulant properties[15]. Brazilin, the main principle of the plant improved the altered immune functions caused by halothane administration in mice. These results might be mainly due to the changes in the function of T cells[26]. Immuno modulation at an initial step of autoimmune diseases is effective to prevent or control the diseases. Brazilin is shown to prevent autoimmune halothane hepatitis by the modulation of altered immune functions in the early phase of halothane intoxicants of C57 BL/6 mice[27]. Several other studies also support the immuno modulating activity of brazilin.

Hypoglycemic activity

Brazilin exhibited potent hypoglycemic action in streptozotocin induced diabetic rats[28]. It improved the glucose metabolism in primary cultured rat hepatocytes, in soleus muscles from rats made diabetic with streptozotocin, and in adipose tissues from diabetic KK mice. It also increased basal glucose transport in $3T_3L1$ fibroblasts and adipocytes, but insulin stimulated glucose transport was not influenced[28].

Anticomplementary activity

The hexane, ethyl acetate and methanol extracts and the sterol fraction of the heartwood exhibited anticomplementary activity. The sterol mixture consisting of campesterol, 11.2; stigmasterol, 18.9; and β-sitosterol, 69.9% was the most potent. The isolated compounds brazilin, brazilein and protosappanin E also exhibited anticomplementary activity[29].

Hepatoprotective activity

Brazilin reduced $BrCCl_3$ induced toxicities on rat hepatocytes *in vitro* indicating the hepatoprotective nature. It also showed a protective role on the $BrCCl_3$ induced depression of microsomal calcium sequestration activity[30]. The water extract of the wood exhibited glutamate pyruvate transaminase stimulation effect at 1 mg/ml concentration against CCl_4 induced hepatotoxicity in rat hepatocytes[31].

Other activities

The heartwood along with several other plants was given orally in powdered form 5-7 g t. i. d. for 2 months to 138 patients suffering from intestinal metaplasia and atypical hyperplasia of the gastric mucosa of chronic gastritis. The formulation was found very effective therapeutically[32]. The chloroform and hot water extracts of the wood showed significant inhibition of phosphodiesterase at 100mg/ml concentrations[33-34]. Ethanol extract of the wood exhibited melanin formation stimulation and tyrosinase stimulating properties[35]. These results support the traditional use of sappan wood for improvement of complexion. Out of the 142 extracts of traditional herbs studied *in vitro* for antimeasles activity, sappan wood was found to be the most potent.

The methanol extract of the heartwood exhibited sleeping time prolonging effect when given (i.p.) to mice[36]. Protosappanin A extended the sleeping time of mice induced by hexobarbital (80 mg/kg) at the dose of 42 mg/kg i.p., but its activity is relatively weak when compared to the methanol extract[37]. The methanolic extract and two purified compounds, brazilin and hematoxylin isolated from the wood showed a significant and dose dependent vasorelaxing effect via NO and subsequent cGMP formation[38]. The sappan wood is found to be a potent agent for the inactivation of human sperms *in vitro*. However, the activity is concentration dependent, and about 2.4 mg/ml is required to reduce motility to 50% of the control medium[39]. The 50% ethanol extract of the dried stem showed semen-coagulating effect on rat sperms[14].

Water extract of the wood showed anticoagulant activity in mice at a dose of 0.1 g/kg body weight[40] and anti-anaphylactic activity at 1 µg/ml concentration on complex induced degranulatation of biotinyl IG_E-Avidin β-hexosaminidase from rat basophilic leukemia cells[41]. The methanol extract of the plant demonstrated predominant antihypercholesteremic activity and two aromatic compounds structurally related to brazilin are found to be responsible for the activity[42]. It also showed inhibition of histamine release from the mast cell at 250µg/ml concentration[43]. Methanol extract of sappan wood showed remarkable anticonvulsant activity. Its ethyl acetate fraction significantly inhibited the activities of GABA degradative enzymes, succinic semialdehyde dehydrogenase (SSADH) and succinic semialdehyde reductase (SSAR). Sappan chalcone and brazilin were the active compounds isolated from this fraction[44].

Chemical constituents

A great deal of chemical investigation has been carried out on heartwood and other parts of the plant and the presence of compounds, viz. triterpenoids, flavonoids, oxygen heterocycles, lipids, steroids and amino acids in the heartwood and seeds has been reported. Brazilin, the main constituent of the plant is oxidized to produce brazilein by air and light[45]. Caesalpin J and P, protosappaninn A, B, C, E_1 & E_2 and sappanin are the other oxygen heterocycles isolated from the wood[42]. Protosappanin A is a metabolite of sappan chalcone and the precursor of sappanin[36]. Several flavonoids and homo-isoflavonoids are also reported from the heartwood. These include ombuin, quercetin, rhamnetin, sappan chalcone, sappanol and its ethers, 8-methoxy bonducellin, caesalpinia chromans, chromanones and chalcones. The biogenetic pathway from sappan chalcone to brazilin via three known homo-isoflavonoids is known[42, 46].

Apart from these constituents triterpenes (β-amyrin, taraxerol), stearic acid, palmitic acid, β-sitosterol have also been isolated from the heartwood. The seed oil contains lupeol, β-amyrin, stigmasterol and fatty acids. Major fatty acids are: linoleic, 31.60, oleic, 27.30, palmitic, 18.76 and linolenic, 14.75 per cent[3].

Conclusion

Based on the literature it can be concluded that ***Caesalpinia sappan*** heartwood has high potential for therapeutic and colouring use. It is being used in Kerala, India and several parts of the world for its medicinal properties. These aspects and its high LD_{50} value[14] indicate its safety and non-toxicity. Reported activities confirmed its antitumor antimicrobial, antiviral, anti-inflammatory, hepatoprotective and several other properties. Studies carried out in our laboratories proved its strong antioxidant properties[47]. As a colouring agent in wines, meat and fabrics its use is already well established[3]. It can be used as a colouring agent for food products and for pharmaceuticals safely. The dye can be made use for colouring foods such as hard cheese, butter, other dairy products, fish products, salad dressing, confectionary, bakery, ice-creams, beverages, snack foods, floor polishes, etc. It can also be used in the preparation of shoe polish, hair nails, red ink, stain for fine wood finishing and for colouring leather, furs, silk and toys. It has a potential to enter the market as a herbal antioxidant mineral water, as being used commonly in Kerala.

Development of effective and nontoxic radio-protecting agent is of considerable interest for radiation medicine, space-flights, nuclear industries and emergencies. A large number of chemical and biological agents have been screened in this connection, but most of them possessed severe side effects and restricted their use. Since the heartwood is capable of giving protection from UV rays and also possesses strong antioxidant activity, it can be developed as an effective radio-protective agent. It can be used in skin care products in cosmetics. Apart from its colouring aesthetic effects, the consumers shall get the beneficial medicinal effects of this wood on their body and such colorants are in demand now.

In future, more basic research is needed to elucidate the mechanism of actions and isolation of its active ingredients. ***C. sappan*** with highly interesting biological effects and vast folklore uses is worth studying more and that might provide a rich natural resource of lead compounds for drug development. Brazilin, responsible for most of the biological effects of the wood, has the potential to become a drug to enter into the market.

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