

Phytochemical and Pharmacological Aspects of *Caesalpinia sappan*

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ABSTRACT

In spite of many synthetic compounds, the most efficient drugs available have their roots directly or indirectly related with the plant kingdom. Many of the extracts have proven to possess pharmacological action. *Caesalpinia sappan*, a plant widely used in the traditional medicinal systems of India has been reported to possess antibacterial, anti-inflammatory, antioxidant, anticancer and immunosuppressive activities. This review highlights some of the phytochemical and pharmacological aspects.

Key words: Phytochemical, Pharmacological, *Caesalpinia sappan*

INTRODUCTION:

Caesalpinia sappan (Caesalpinaceae) is a small thorny tree, 6-9m in height and 15-25 cm in diameter with a few prickly branches. It is commonly known as Patag. In English known as Sappan wood, Brazil wood. The tree grows wild, in mountains and is cultivated in the gardens for its large panicles of yellow flowers. The tree was formerly cultivated in South-East Asia for the red dye, obtained from its heartwood¹. *C. sappan* is distributed in Tamilnadu, Kerala, Karnataka, Andhra Pradesh and West Bengal². The leaves of *C. sappan* are compound, with 8-12 pairs of oblong leaflets and small prickles. Flowers are yellow in terminal and axillary panicles, fruits are woody pods, sub compressed with a hard recurved short beak. Seed are 3-4, yellowish-brown. Wood is orange-red, hard, very heavy (wt, 1.073 kg/m³, air dry), straight-grained with a fine texture³. No comprehensive review article on both the chemical and biological aspects of *C. sappan* has appeared so far. Hence, an attempt was made by us to

enumerate the phytochemical and pharmacological aspects in this article.

THERAPEUTIC USES

The wood is bitter, dry, sour, cooling; cure "Vata", biliousness, fever, delirium, ulcers, strangury, urinary concentration and blood complaints. It is considered astringent and sedative. It is useful in vitiated conditions of *pitta*. An infusion of the wood is a powerful astringent and emmenagogue. It is used in atonic diarrhea and dysentery, and its paste in rheumatism, hemorrhages and to treat wounds.

Hot aqueous extract and chloroform extract of wood exhibited inhibitory action on cyclic AMP phosphodiesterase. The methanolic extract of the sappan lignum showed sleep time-elongation effect in mice and significant anti-hypercholesteremic activity. Brazilin dye is reported to have anti-inflammatory activity⁴.

The trunk wood possesses antibacterial, demulcent and haemostatic properties. It is used in contusion, wounds, dysmenorrhoea, colic furnuculosis, impetigo, leucorrhoea and anemia. "The plant is one of the ingredients of an indigenous drug 'Lukol' which is administered orally for the treatment of non-specific leucorrhoea"⁵.

PHYTOCHEMICAL CONSTITUENTS

The wood is reported to contain a glycoside containing β -amyirin, glucose and the free amino acids: alanin, aspartic acid, glycine, praline, valin, leucine, threonine; free sugars: lactose, galactose, 2-deoxyribose and glucose also present^{6,7}.

Heartwood contains several aromatic compounds, brazilin, sappanchalcone, caesalpin J, caesalpin P, protosappanin A, protosappanin B, homoisoflavonoids β -sitosterol and presence of monohydroxybrazilin and benzyl dihydrobenzofuran derivatives is also reported in the lignum. it also contains sappanol, episappanol, 3'-deoxysappanol, 3'-0-methylsappanol, 3'-0-methylepisappanol, 3'-0-methylbrazilin, 4-0-methylepisappanol, sappanon β , 3-deoxysappanone β , 3'-deoxysappanone β and dibenzoxocin derivative, 10-0-methyl-protosappanion β . Presence of 4,4'-dihydroxy-2'-methoxychalcone, 8-methoxy-bonducellin, quercetin, rhamnetic and ombuin is also reported⁸.

Three new homoisoflavonoids, 7-hydroxy-3-(4'-hydroxy-benzylidene)-chroman-4-one, 3,7-dihydroxy-3-(4'-hydroxy-benzyl)-chroman-4-one and 3,4,7-trihydroxy-3-(4'-hydroxy-benzyl)-chroman were isolated from the dried heartwood together with the known compounds 4,4'-dihydroxy-2'-methoxychalcone, 8-methoxybonducellin, quercetin, rhamnetin and ombuin⁹.

A novel lactone, brazilide A has been isolated from an oriental crude drug, the heartwood of *C. sappan* and its structure was established by spectroscopic analysis and X-ray crystallography¹⁰. Dong Seon Kion et al reported the ¹H and ¹³C NMR signals of brazilin.

Two new aromatic compounds structurally related to brazilin were isolated and identified from the

heartwood .they possessed antihypercholesteremic activity¹¹.

A novel dimeric methanodibenzoxocinone, named neosappanone A possessing a unique unprecedented novel carbon framework, has been isolated from the heartwood and its structure was elucidated on the basis of spectroscopic analysis. Neosappanone competitively inhibited xanthine oxidase in a concentration –dependent manner. A novel biogenetically exclusive benzindenopyran, with a new carbon framework, neoprotosappanin and a new compound protosappanin A dimethyl acetal, were isolated together with protosappanin E-2, neosappanone A and previously reported phenolic compound¹².

The woody part contains brazilin and brazilin. These are the main constituents of brazilwood were studied by vibrational spectroscopic study¹³. Dong Seon Kion et al reported the ¹H and ¹³C NMR singals of brazilin¹⁴. The sterol mixture (campesterol 11.2%, stigmasterol 18.9% and β -sitosterol 69.9%), brazilin, brazilin, and protosappanin E isolated from *C. sappan* heartwood¹⁵. An essential oil consisting of D-a-phellandrene, oscimene tannin gallic acid and saponin¹⁶.The pods contain 40% tannins and it can be used in place of sumac. They impart a uniform tan and soft touch to the leather and can be used in mixed chrome tannages¹⁷.The essential oil with a pleasant odour is found in the leaves. The oil contains d-a-phellandrene and oscimene^{18,19}.

The seeds contain 7% protein. The amino acids present in the seed-protein are: alanine, cystine, glycine, isoleucine, lysine, threonone, tryptophan and valine. Petroleum ether extract of seeds give orange colored fixed oil (18%). The fatty acid content: capric, lauric, myristic, myristoplalmatic, palmitic, palmitoleic, oleic, linoleic, linolenicv and arachidic acids. The fixd oil is a potential ingredient of paints²⁰.

Two compounds were such as tetraacetylbrasilin and protosappanin isolated from the stem of *C. sappan*²¹. Sappanchalcone is isolated from *C. sappan*, the proposed biosynthetic precursor of brazilin²².Beak NI et al reported that sappanchalcon and brazilin were isolated from ethyl acetate extract of wood of *C. sappan*²³.

Two compounds were isolated from *C. sappan* cell (control group) in the presence of chloroform extract. L by multiple steps of column chromatography and thin layer chromatography. Structures of the two compounds were determined by spectroscopic methods as 1',4'-condensation and shrinkage of nuclei in the HNSCC4 and dihydro-spiro[benzofuran-3(2H),3'-[3H-2]benzopyran]-HNSCC31 cells. The levels of P⁵³ and P²¹ WAF1/CIP1 1',6',6',7'-tetrol and 3-[[4,5-dihydroxy-2(hydroxymethyl)phenyl]-methyl]-2,3-dihydro-3,6-benzofurandiol²⁴. Four compounds, A, brazilin and caesalpin J, isolated from *C. sappan*²⁵, which is linked to increased cellular levels of P⁵³ and P²¹ WAF1/CIP1³².

Isolation of the red dye using both conventional and newly developed microwave method was carried out by Badami.S et al. The conventional heating of 2 h provided 0.656 +/- 0.049 g of the dye and by microwave heating at 540 W for 20 min, the yield obtained was 0.747 +/- 0.047 g²⁶. Natural red dyes in old Indian textiles are evaluated by thin-layer chromatographic systems²⁷.

Phenolic compounds mainly included phenolic acids, flavonoid, tannins, coumarins, lignans, quinones, stilbenes, and curcuminoids are isolated from different traditional medicines including *C. sappan*²⁸.

PHARMACOLOGICAL ACTIVITIES

Antioxidant Activity: Antioxidant activity of *C. sappan* heartwood was studied both by in vitro and in vivo models. The ethyl acetate, methanol and water extracts exhibited strong antioxidant activity as evidenced by the low IC₅₀ values in both 1,1-diphenyl-2-picryl hydrazyl (DPPH) and nitric oxide methods. Administration of the successive methanol and water extracts at 50 and 100 mg/kg body weight given for 4 days prior to carbon tetrachloride (CCl₄) treatment caused a significant increase in the level of superoxide dismutase (SOD) and catalase and a significant decrease in the level of thiobarbituric acid reactive substances (TBARS), when compared to CCl₄ treated control in both liver and kidney. These changes observed at 100 mg/kg body weight treatment were comparable to those observed for standard vit E at 50 mg/kg treatment²⁹. Ethyl acetate extracts of *C. sappan* show the antioxidant activity³⁰. Brazilin is an antioxidative substance and it has a protective effect on the BrCCl₃-induced depression of microsomal calcium sequestration activity³¹.

Anticancer Activity: The chloroform extract of *C. sappan* induces cell death in head and neck cancer cell. The viability of HNSCC4 and HNSCC31 cells (head and neck cancer cell lines) was noticeably decreased compared to that of HaCat

Anticancer effect of methanol extract on oral carcinoma (KB) and osteosarcoma (HOS) cells were investigated. It seems that the anticancer effect is at least partially due to telomerase inhibitory effect. Dichloromethane, n-hexane and ethyl acetate fractions were screened for anticancer activity, from these the highest anticancer activity was found in dichloromethane fraction which had IC₅₀ value of 4.4 and >4.0 ug/ml against oral carcinoma (KB) cells and osteosarcoma (HOS) cells, respectively³³. An ethyl acetate extract of the heartwood of *C. sappan* exhibited potent DNA strand scission activity³⁴.

Anti-inflammatory Activity:

C. sappan shows anti-inflammatory activity by inhibition of prostaglandin biosynthesis and nitric oxide production³⁵. Brazilin has been known as a natural red pigment. It exhibited the inhibitory effect on lipopolysaccharide (LPS)-stimulated NO production in a dose dependent manner. It suggests that the suppressive effect of isoform of nitric oxide synthase gene expression by brazilin might provide one possible mechanism for its anti-inflammatory and cancer chemopreventive activity³⁶. Brazilin forms a complex with Cu (II) in the presence as well as the absence of DNA. The Cu (II)-brazilin complex exhibited the strand cleavage activity for the pBR322 supercoiled DNA, converting supercoiled forms to nicked form. The presence of various scavengers for the oxygen species suppresses or reduces the cleavage activity of the complex, indicating that the DNA cleavage is oxidative³⁷. Administration of brazilin after onset of cerebral ischemia reperfusion can reduce the brain infarction area and improve the neurological score. The mechanism underlying the action was investigated and attributed to the anti-inflammatory effect of brazilin³⁸.

Immunosuppressive Activity:

Heartwood of *C. sappan* has been used in Chinese medicines for treating a variety of immune-mediated pathology and inflammatory disease. Brazilein and ethanol extract could distinctly inhibit the proliferation of T lymphocyte stimulated by Concanavalin A (Con A) and the proliferation of B lymphocyte stimulated by lipopolysaccharides (LPS) and brazilein could suppress mice humoral immune response by plaque forming cell (PFC) test. Brazilein can induce apoptosis in mice spleen lymphocytes by flow cytometry analysis and DNA fragmentation assay, which may be one of the pathway that brazilein inhibited immunocompetence of mice lymphocytes³⁹.

Antidiabetic Activity:

Brazilein, active component of sappan wood, decreases blood glucose in diabetic animals. Brazilein inhibits hepatic Gluconeogenesis by elevating the F-2, 6-BP level in hepatocytes, possibly by elevating cellular F-6-P/H-6-P levels and PFK-2 activity. Increased pyruvate kinase activity may also play a role in the anti-gluconeogenic action of brazilein⁴⁰.

Antimicrobial Activity:

Antimicrobial activity of *C. sappan* against clinical isolate of methicillin resistant *staphylococcus aureus* (MRSA) and effect of *C. sappan* extract on the invasion of MRSA to human mucosal fibroblasts (HMFs) was studied. Chloroform, n-butanol, methanol and aqueous extracts showed antimicrobial activity against standard methicillin-sensitive *staphylococcus aureus* as well as MRSA. In dilution method methanol extract markedly lowered the minimal inhibitory concentration (MICs) of ampicillin and oxacillin against MRSA. Here methanol extract may have antimicrobial activity and the potential to restore the effectiveness of β -lactum antibiotics against MRSA and inhibit the MRSA invasion to HMFs⁴¹. *C. sappan* also shows the antibacterial activity⁴².

Vasorelaxing Effect:

Methanolic extract and two purified compounds (brazilein and hematoxylin) from *C. sappan* were

examined for their relaxant effects in isolated rat thoracic aorta. The methanolic extract significantly and dose-dependently relaxed the α -receptor against phenylphrine-precontracted aortic rings, without affecting passive tension of these vessels. Removal of the vascular endothelium, inhibition of nitric oxide (NO) synthase with 0.1 mM N^w-nitro-L-arginine and of cGMP biosynthesis with 10 μ M Methylene blue abolished the vasorelaxant effect of the herbal extract at doses up to 30 μ g/mi. similar vasorelaxant effects were observed with brazilein and hematoxylin⁴³.

The vasorelaxant activity of *C. sappan* was investigated in isolated rat aorta and human umbilical vein endothelial cells. Brazilein induces vasorelaxation by the increasing intracellular Ca(2+) concentration in endothelial cells of blood vessels and hence activating Ca(2+)/calmodulin-dependent NO synthesis. The NO is released and then transferred into smooth muscle cells to activate guanylyl cyclase and increase cGMP content, resulting in vasorelaxation⁴⁴.

Antiproliferative Activity:

Methanol, methanol-water (1:1) and water extract of *C. sappan* showed selective activity against human cervix HeLa adenocarcinoma, human lung A549 adenocarcinoma, murine colon 26-L5 carcinoma, murine Lewis lung carcinoma (LLC) and murine B16-BL6 melanoma cells. Characteristic morphological change and DNA fragmentation indicated the antiproliferative activity to be due to the induction of apoptosis⁴⁵.

Antiplatelet Activity:

Brazilein, the major component of *C. sappan* was reported to show antiplatelet activity through the inhibition of phospholipase A₂ (PLA₂) activity and the increase in intracellular free Ca²⁺ concentration ([Ca²⁺]_i), its derivatives such as BRX-018, (6*aS,cis*)-Malonic acid 3-acetoxy-6*a*9-bis-(2-methoxycarbonyl-acetoxy)-6,6*a*,7,11*b*-tetrahydro-indeno[2,1-*c*]chromen-10-yl ester methylester, was confirmed as one of the potential antiplatelet agents. Its antiplatelet activity may be based on the inhibitory mechanisms on TXA₂ synthesis in stimulated platelets⁴⁶.

Analgesic Activity:

The ethanol extract of heartwood and three crude fractions (petroleum ether (60-80°C), diethyl ether and ethyl acetate) were subjected to pharmacological screening for analgesic activity using acetic acid-induced writhing in albino mice. The ethanol extract of heartwood and three crude fractions were found to show peripheral analgesic activity⁴⁷.

Acaricidal Activity:

Acaricidal effect of material derived from *C. sappan* heartwood against *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* were assessed and compared with those evidenced by commercial benzyl benzoate and DEET. The LD (50) values of the methanol extracts were 6.31 and 5.44 µg/cm (3) against *D. farinae* and *D. pteronyssinus*, respectively. Furthermore, the ethyl acetate fraction derived from the methanol extract was approximately 8.71 more toxic than DEET against *D. farinae* and 4.73 time more toxic against *D. pteronyssinus*. From ethyl acetate fraction juglone (5-hydroxy-1, 4-naphthoquinone) was isolated. This indicated that the acaricidal activity of *C. sappan* heartwood is due to the effects of juglone. Accordingly, juglone should prove to be quite useful as a potential control agent, lead compound and house dust mite indicator⁴⁸.

Miscellaneous:

Sappan wood promotes blood circulation and removes blood stasis and cause subsidence of swelling and relieves pain. 5-hydroxy-1, 4-naphthoquinone isolated from heartwood of *C. sappan*, when it is tested with *Clostridium perfringens*, it produced the strong (+++) inhibition at 5 and 2 mg/disk and moderate (++) inhibition at 1, 0.5 and 0.25 mg/disk. Furthermore this isolate revealed a weak (+) growth inhibition against *Lactobacillus casei* at 5 and 2 mg/disk. It indicates that hydroxyl fractional group of naphthoquinone seems to be required for selective growth-inhibiting activity against *C. perfrings*. Accordingly the compound derived from *C. sappan* heartwood could be useful as a preventive agent against diseases caused by *C. perfringens*⁴⁹.

C. sappan extract from a study of screened Chinese herbal medicines was found to be a potent agent for the inactivation of human sperm in vitro. Exposure of sperm from healthy donors to this agent showed remarkably

reduced sperm motility. The antimotility effect of *C. sappan* is concentration-dependent and about 2.5 mg/ml is required to reduce motility to 50% the control medium (EC50). This result suggests that this traditional Chinese herbal medicine possesses an antimotility effect on human sperm in vitro and has the potential of becoming in the future a new and acceptable male oral contraceptive⁵⁰. Brazilin show the effect on glucose transport into isolated rat epididymal adipocytes. It may increase glucose transport by recruitment of GLUT4 from intracellular pools to the plasma membrane of adipocytes via the activation of PI3-kinase⁵¹.

Brazilin increased [³H] 2-deoxyglucose uptake in isolated rat epididymal adipocytes. The fact that calcium may be required for the stimulatory effects of insulin on glucose transport suggests that brazilin might also require calcium for its glucose transport-stimulating action. Therefore maintenance of the intracellular calcium concentration, rather than an increase in it, may be essential for the stimulatory action of brazilin on glucose transport⁵².

CONCLUSION

Caesalpinia sappan may be considered as a valuable plant in both ayurvedic and modern drug development areas of its versatile medicinal uses. Emphasis has been laid on the pharmacological activity of brazilin and brazilin.

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