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PHYTOCHEMISTRY AND PHARMACOLOGY OF *SANTALUM ALBUM* L.: A REVIEW

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ABSTRACT

Santalum album L. (Santalaceae) commonly known as Indian Sandalwood is one of the oldest and precious sources of natural fragrance with immense medicinal and commercial significance. *S. album* has been grown in India for the last 25 centuries and esteemed all over the world for its sweet, long-lasting and medicinally valued fragrant oil. Sandalwood and the essential oil derived from sandal heartwood have been used in various traditional systems of medicine, like Ayurveda, Siddha and Unani medicine in the treatment and prevention of wide range of ailments. The versatile therapeutic and healthcare importance of sandawood is attributed to the rich source of phytochemicals particularly sesquiterpeness. A thorough bibliographic investigation was carried out by analyzing worldwide accepted scientific database (Pub Med, SciFinder, Scopus, ACS and Web of Science), recognized books, Indexed as well as non indexed journals. Modern pharmacological studies have demonstrated a wide range of pharmacological activities ranging from antibacterial to anti-cancer. No significant toxicity has been indicated by sandalwood oil and its individual constituents, however, further study on chemical constituents and their mechanisms in exhibiting certain biological activities are needed to understand the full phytochemical profile and the complex pharmacological effects of this plant. The increased commercial exploitation of Sandalwood and low productivity of this endangered plant has raised the concern over its conservation and productivity enhancement through modern tools and techniques. The review discusses traditional uses, ethnopharmacology, phytochemistry and biological activities of sandalwood in order to divulge its medicinal and industrial worth and gaps requiring future research.

KEY WORDS: *Santalum album*, Ethnopharmacology, Phytochemistry, Biological activity, Research prospects.

INTRODUCTION

Santalum album L., belonging to the family Santalaceae is one of the most precious trees in the world.[1] Commonly known as White sandalwood (English), Safed Chandan (Hindi) and Srigandha (Sanskrit), it is considered to be a revered endowment of the plant kingdom woven into the culture and heritage of India. Acclaimed as one of the oldest known perfumery materials having more than 2000 years of incessant history, sandalwood has retained its eminence as admired perfumery stuff from antiquity down to modern times. Historical review reveals that sandalwood has been referred in Indian mythology, folklore and ancient scriptures. Certain cultures place great significance on its fragrant and medicinal qualities. It is generally accepted that sandal is indigenous to peninsular India as its history of recorded occurrence dates back to at least 2500 years. Sandal tree grows under different edaphic and eco-climatic conditions, adapts very well in terms of growth, heartwood and oil content.[2] The finest wood grows in driest region particularly on red or stony ground while on rocky ground the tree often remains small but gives the highest yield of oil. The heartwood is moderately hard, heavy, durable, yellow or brown in appearance, with an oily texture and is an exquisite material for carving intricate designs. The carved images of gods and mythological figures have a high demand in the market. A wide variety of articles such as boxes, cabinet panels, jewel cases, combs, picture frames, hand fans, pen holders, card cases, letter openers and bookmarks are made from sandalwood. The heartwood constitutes the central part of the tree and is valued for its fragrance. The bark and outer wood (sapwood) or other parts of the tree however, have no fragrance. The plant has been mainly exploited for sandalwood oil obtained by steam distillation of its heartwood. Roots also contain essential oil.[3] The yield and quality of oil varies depending on the locality, age of the tree and distillation method. Sandalwood is commercially known as the East Indian sandalwood and its oil the East Indian sandalwood oil.

PLANT DESCRIPTION

Santalum album is an evergreen tree that grows up to 20 m attaining girth of up to 2.4 m with slender drooping branchlets. There are two major commercial species of Sandalwood named Indian Sandalwood (*S. album*) and Australian Sandalwood (*S. spicatum*). Australian Sandal trees are shorter in height. Bark of the tree is tight, dark brown, reddish, dark grey or nearly

black, smooth in young trees, rough with deep vertical cracks in older trees, red inside. The sapwood is white and odourless whereas heartwood is yellowish to dark brown and strongly scented. Leaves thin, usually opposite, ovate or ovate elliptical, 3-8 x 3-5 cm, glabrous and shining green above, glaucous and slightly paler beneath; tip rounded or pointed; stalk grooved, 5-15 cm long; venation noticeably reticulate. Flowers purplish-brown, small, straw coloured, reddish, green or violet, about 4-6 mm long, up to 6 in small terminal or axillary clusters, unscented in auxiliary or terminal, paniculate cymes. Fruit a globose, fleshy drupe; red, purple to black when ripe, about 1 cm in diameter, with hard ribbed endocarp and crowned with a scar, almost stalkless, smooth, single seeded.[4] Flower panicles appear from March to April in India, and fruits ripen in the cold season. In Australia flowers appear in December to January and also June to August, and fruits mature during June to September. The species is spread rapidly through seed dispersal. Viable seed production occurs when the tree attains age of 5 years. Trees more than 30 years old may have circumference from 18-38 inches.

Sandalwood tolerates a wide range of site conditions and grows naturally in a variety of localities in tropical areas, but growth is more vigorous in some conditions than others.[5] *S. album* thrives on well-drained loamy soil preferably on slopes of hills exposed to the sun. It requires a minimum of 20-25 inches rainfall per year. It does not tolerate frost or water-logging, but is drought-hardy and is a light demander in sapling and later stages. Prolonged drought and fire kill trees. The plant is mainly exploited for fragrant sandalwood oil.

HISTORICAL BACKGROUND

There are references to sandalwood in Indian mythology, folklore and scripture. It is mentioned in the Indian literature as old as Milinda Pahna (200 BC), Patanjali Mahabhasaya (100 BC), Dhamma Pada, Anguttara, Vinaya Pitaka (400-300 BC). Kautilya described a variety of sandalwood in his Arthasastra (200 BC). Sandalwood is also mentioned in the epic Ramayana and Mahabharata. It is unlikely that some of the references to sandalwood in the ancient Indian literature pertain to *Pterocarpus santalinus*, called the Red sanders or Red Sandal wood. There is a mass of evidence that *S. album* has been grown in India for the last 25 centuries. The sandalwood oil is esteemed all over the world and India has been main exporting country. Known as ‘Bai tan xiang’ in China, ‘Byaku-dan’ in Japan, Sandalwood has also been known not only in ancient Sanskrit texts and manuscripts but also ancient Chinese ones. It is also used in many forms of initiation rites to open the disciples mind to

receive consecration. In the Zoroastrian Temples it burns in there sacred fires to soothe the troubles of all humanity. It is used by the Jewish, the Buddhist, the Hindus, as well as almost every other belief system for its vast diversity in attributes.[6-7]

ORIGIN AND DISTRIBUTION

S. album is indigenous to the tropical belt of the Indian peninsula, eastern Indonesia and northern Australia. The main distribution is in the drier tropical regions of India and the Indonesian islands of Timor and Sumba. It is a native of the highlands of southern India where the principal sandal tracts are most parts of Karnataka and adjoining districts of Maharashtra, Tamil Nadu and Andhra Pradesh. The species is mostly found in dry deciduous and scrub forests in these regions. The vegetation type is a typical monsoon vine thicket growing on pure sand. It has been recorded on coastal sand dunes immediately above the normal high water mark and close to the mangroves. It also grows on low lateritic cliffs above the beach. The tree is actually an obligate hemi parasite plant on various hosts, *Cassia siamea, Pongamia glabra* and *Lantana acuminata*. It is now planted in India, China, Sri Lanka, Indonesia, Malaysia, the Philippines and Northern Australia.

TRADITIONAL USES

S. album is mainly grown for its timber and fragrant oil. The timber weighing 870 kg/cubic m is durable and strong. Its close grained heartwood is used for ornamental and carving work. The wood has been used as a fuel but is generally considered too valuable for this purpose. Sandalwood oil distilled from the heartwood is a pale yellow to yellow viscous liquid, with sweet, fragrant, persistent, spicy, warm, woody, animalic, milky and nutty notes.[2] It is extensively used in perfumery, cosmetics, aromatherapy and pharmaceutical industry. Being good fixatives, it is highly valued in perfumery and toiletry industry, especially for certain delicate scents that are extremely rare and fragile. No composition of the heavy or oriental type of perfume is complete without an ample dose of sandalwood oil. Most Indian attars use sandal oil as the base because of its inherent capacity to absorb most of the ethereal notes of other whole herbs or flowers, as it can enhance their perfumery status and stability. The oil is used as a flavouring substance in food products such as frozen dairy desserts, candy, pan masala, baked food, gelatine, puddings and also in alcoholic and non-alcoholic beverages. US Food and Drug Administration, Flavour and Extract Manufacturers Association Council of Europe and Joint FAO/WHO Expert Committee has approved sandalwood oil for use as food additives.[8]

Its fruits are edible and the seeds contain fatty oil which is suitable for the manufacture of paint. Powdered heartwood is used to make incense sticks, burnt as perfumes in houses and temples, or is ground into a paste and used as a cosmetic. The bark contains about 12-14% tannin and has good potential in the tanning industry. The foliage of *S. album* is palatable to grazing animals. Leaves make good green manure thus help soil improvement.

As medicine, sandalwood is regarded as coolant, sedative, astringent, disinfectant in genitourinary and bronchial tracts, diuretic, expectorant and stimulant. The wood, root, bark and leaves of the plant used for the treatment of the liver disease like jaundice by the tribal healers.[9] It is very beneficial for treating gastric irritability, jaundice, dysentery, tension and confusion and also used as tonic for heart, stomach, liver, anti-poison, fever, memory improvement and as a blood purifier. Various uses mentioned in Ayurveda system about sandalwood are in treatment of various other ailments like diarrhoea with bleeding, intrinsic haemorrhage, bleeding piles, vomiting, poisoning, hiccoughs, initial phase of pox, urticaria, eye infections and inflammation of umbilicus.[8,10] Sandalwood oil, an active substance of agreeable odour employed in the treatment of sub-acute and chronic infections of mucous tissues, particularly gonorrhoea after the active symptoms have been mitigated. Chronic bronchitis, with fetid expectoration, chronic mucous diarrhoea, chronic inflammation of the bladder and pyelitis are also said to be benefited by it.

ETHNOLOPHARMACOLOGY

Therapeutically, sandalwood has calming and relaxation effect. It is claimed to reduce stress, depression, fear, nervous exhaustion, anxiety, discomfort, and insomnia and enhances meditation. It was believed to promote spiritual practices, peaceful relaxation, openness and grounding.[6] Sandalwood is used in various traditional systems of medicine, like Ayurveda, Siddha and Unani medicine to treat a wide range of ailments. In the Indian traditional medicine system Ayurveda, white sandalwood has largely been used as a demulcent, diuretic, and mild stimulant.[11] In Ayurveda sandalwood is regarded as antiseptic, antipyretic, antiscabietic, diuretic, expectorant, stimulant and prescribed for the treatment of bronchitis, dysuria, urinary infection and gonorrhoea owing to its antibacterial and antifungal properties.[12] Other therapeutic uses mentioned in Ayurveda include its utilization in the treatment of several ailments like biliousness, fever, bleeding piles, diarrhoea with internal bleeding, eye infections, hemorrhage, hiccoughs, inflammation of umbilicus poisoning, initial phase of pox, urticaria and vomiting.[3,8] The aromatic nature of sandalwood is calming to an

aggravated nervous system; it balances *Vyanavayu* and cools *Sadhaka pitta*, making it useful for treating depression and mental disturbance.[13] It is applied externally in the form of paste with water or rose water to skin eruptions, to the temples in headaches, fevers, to skin diseases to allay itching, inflammation, heat and pruritus.[14] In Unani medicine, Safed Sandal is used to treat gastric ulcers. Sandalwood is one of the potential anti-ulcer agents used in Unani system of medicine.[15] Kausar and co-workers reviewed the Unani perspective and recent studies of *S. album*.[16] In the Traditional Chinese medicine (TCM), sandalwood finds its mention as treatment of skin diseases, acne, dysentery, gonorrhea, anxiety, cystitis, fatigue, frigidity, impotence, nervous tension, immune-booster, eczema, stomachache, vomiting and stress. According to Chinese medicine, sandalwood acts in case of any type of chest pains, originating either from lungs or heart. The regulating and dispersing action of the oil is curative of the angina pain. Sandalwood also earns a mention in 'De Materia Medica' written by Greek physician, *Discorides* who is considered as the father of pharmacology.

Pharmacological studies have established that sandalwood and its root bark possessed abortifacient, hepatoprotective, urinary antiseptic, stomachic, anti-viral and anti-herpetic activities.[17] The hydrolyzed exhausted sandalwood powder (HESP) possesses anti-remorogenic, anti-inflammatory, anti-mitotic, antiviral, anti-cancerous, anti-hypertensive, anti-pyretic, sedative, ganglionic blocking and insecticidal properties.[18-19] The soothing and demulcent effects of sandalwood oil have been used to treat respiratory tract infections, specifically chronic bronchitis involving chronic dry cough.[20-22] Recently, apoptotic, cytotoxic, antiviral, and anti-Helicobacter pylori properties have been reported.[23] Bioactive principles having anti-cancer, anti-tumor,[24] anti-viral,[25] anti-*Helicobacter pylori*[26] and cytotoxic santalols as well as lignans [27] are obtained from the heartwood.

Sandalwood oil finds frequent mentions in traditional medicinal systems as diaphoretic, diuretic, carminative, antiseptic, antipyretic, cicatrisant, antiphlogistic, antispasmodic, antiscabietic, expectorant, stimulant and for the treatment of bronchitis, dysuria, psoriasis, palpitations, sunstroke, urethritis, vaginitis, acute dermatitis, urinary infection, gonnorheal recovery as it contains antibacterial and antifungal principles.[28-32] It is used as blood purifier and tonic for heart, stomach and liver, and also in fever and memory improvement.[33] The oil along with other plant mixtures has been used to cure stomach illnesses, elephantiasis and lymphatic filariasis.[34] Venous and lymphatic stasis such as varicose veins and swollen lymph nodes of the lymphatic system were traditionally treated with sandalwood oil, where the

therapeutic potential was attributed to santalols having antiinflammatory effect.[35] The E-monograph by German Commission suggests 1-1.5 g of the sandalwood oil for the supportive treatment of urinary tract infections, fevers and strengthening the heart.[36]

PHYTOCHEMISTRY

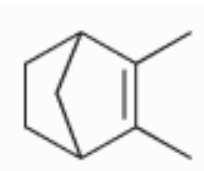
Sandalwood, the major source of costliest wood and essential oil has been extensively investigated for its chemical constituents. Sandalwood oil is accumulated in the heartwood only after 30 years of its growth under natural conditions.[37] The yield and compositions of any essential oil are strongly influenced by the age of the tree, colour of heartwood, organ maturation, individual tree, location within the tree and the environmental cues and the plants genetic factors.[38-40] Traditionally, as an age-old practice the steam distillate of the heartwood is sold as marketable sandalwood essential oil. The essential oil yield from an old matured tree ranges from 2.5-6% depending on the age of the tree, colour of the heartwood, individual tree under study, location within the tree and the environment of growth of the tree.[41-42] Moreover the compositions of oil obtained from young and mature sandal trees varies[43] while the content and composition of oil varies from heartwood sampled at different levels in the tree.[44]

Sandalwood oil has been extensively studied for the chemical constituents and their isolation, synthesis and quantitative estimation.[45-57] Considerable work was done by Shankaranarayana and co-workers on phytochemical and other related aspects of sandalwood including separation of α- and β-santalols by column chromatography,[58] chromatographic separation of alpha and beta santalenes,[59] simple method for extracting sandal oil in higher yield through rectification of benzene extract,[60] preparation of sodium santalbate-dimethyl sulfate inclusion complex,[61] estimation of oil in depot based sapwood of sandal,[62] possibility of developing fragrant products from less odorous sandalwood oil,[41] estimation of content and composition of oil from central and transition zones of sandal disc,[63] utilization of sandalwood extractives,[64] recovery of essential oil from hydrolyzed exhausted sandalwood powder (HESP)[65-66] and isolation of santalols from sandalwood oil.[67]

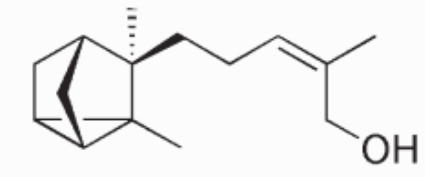
Major constituents of commercially available sandalwood oil are sesquiterpene alcohols like α- and β-santalols ($C_{15}H_{24}O$), bergamotols and several of their stereoisomers, whereas minor constituents includes lanceol, nuciferol, bisabolol and the sesquiterpene hydrocarbons such as α-and β-santalenes ($C_{15}H_{24}$), bergamotenes, α-, β- and γ-curcumenes, β-bisabolene[68-72] and phenylpropanoids.[73] Usually, α-santalol is more abundant than β-santalol.[74] Verghese and

co-workers reported sesquiterpene alcohols, cis-α-santalol and cis-β-santalol, α-trans-bergamotol, epi-cis-β-santalol as major essential oil components.[75] Minor constituents include trans-β-santalol and cis-lanceol,[72] hydrocarbon santene (C_9H_{14}), α-santalene, β-santalene, α-bergamotene, epi-β-santalene, α-curcumene, β-curcumene, γ-curcumene, β-bisabolene, α-bisabolol[72,76] and heterocyclics.[77] The other constituents reported in the sandalwood oil includes alcohol, santenol ($C_9H_{16}O$) and teresantalol ($C_{10}H_{16}O$); the aldehydes, nor-tricycloekasantalal ($C_{11}H_{16}O$) and isovaleraldehyde; the ketones, l-santenone ($C_9H_{14}O$) and santalone ($C_{11}H_{16}O$) and the acids, teresantalic acid ($C_{10}H_{14}O$) occurring partly free and partly in esterified form and α- and β-santalic acids ($C_{15}H_{22}O_2$). Genetic diversity among Sandal populations of different provenances in India[78] as well as relationship between girth and heartwood/oil yield in Sandal provenances[2] were studied. Although both Indian as well as Australian sandalwood oils contain similar components, the concentrations of these components are different, creating two similar but quite distinctive oils. Main constituents in Australian Sandalwood oil are sesquiterpenes dominated by the two primary sesquiterpene alcohols, α-santalol and β-santalol along with both E, E-farnesol and α-bisabolol.[79]

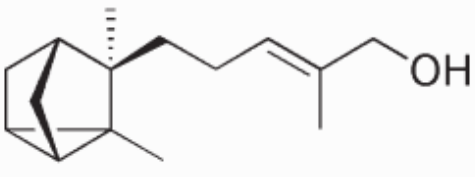
It is worth mentioning here that content of secondary metabolites depends on the inherent characteristics of plant material, environmental, and genetic aspects, or by extrinsic aspects such as extraction methods.[80] It was also mentioned that quantity of santyl acetate and santalene in a 10 year old tree are slightly more than in a 30 year old tree.[81] Roots of East Indian Sandalwood tree were also examined for yield and composition of essential oil. Recovery of oil from roots was recorded to be 10.3% through solvent extraction of sandalwood. GC and GC/MS analysis of oil led to the detection of fifty-three compounds representing 99.9% of the total oil, including 30 sesquiterpenols (78.5%), 9 sesquiterpenes (7.8%), a terpenoic acid (0.4%) and 5 sesquiterpenoid isomers (4.4%).



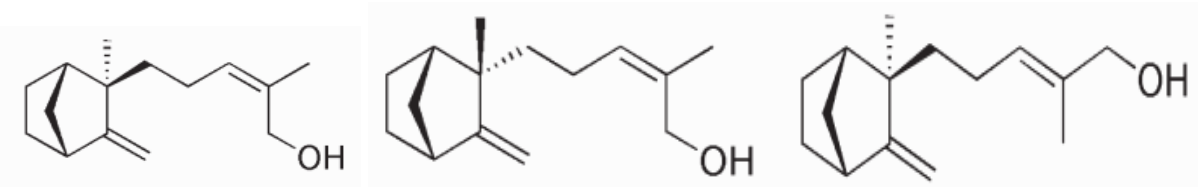
Santene



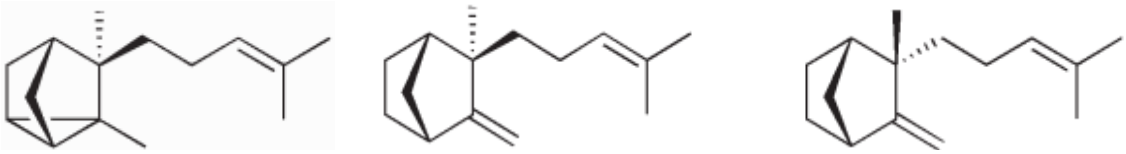
(Z)-α-Santalol



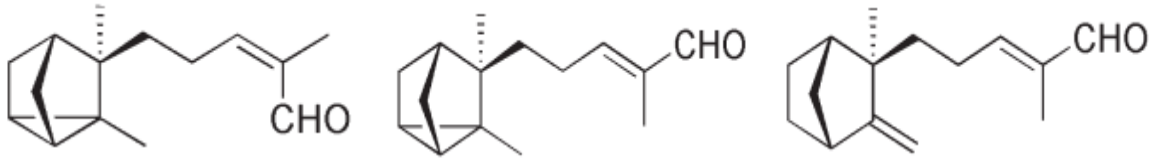
(E)-α-Santalol



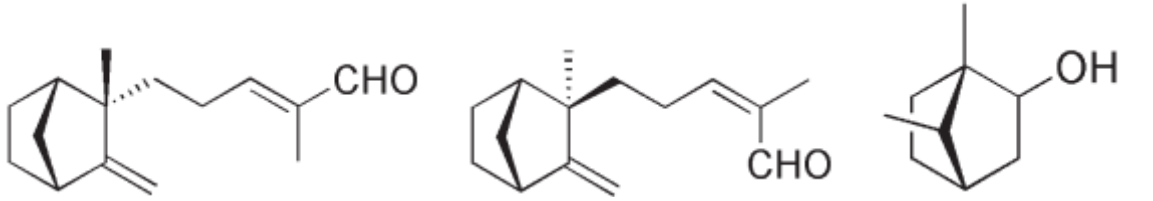
(Z)-β-Santalol **epi-(Z)-β-Santalol** **(E)-β-Santalol**



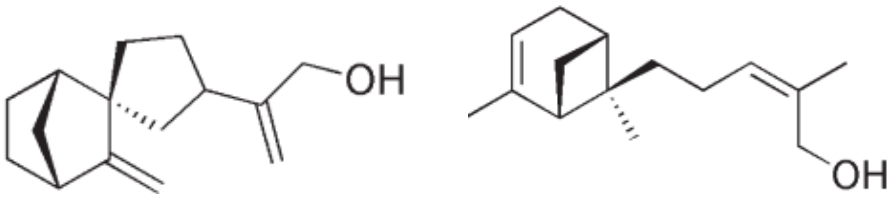
α-Santalene **β-Santalene** **epi- β-Santalene**



(Z)-α-Santalal **(E)-α-Santalal** **(E)-β-Santalal**



(E)-epi-β-Santalal **(Z)-β-Santalal** **α-Santenol**



Spirosantalol **(Z)-α-trans-Bergamotol**

The major constituents in the essential oils were α- and β-santalol, accounting for 19.6 and 16.0%, respectively. The content of α-santalol was less than a proposed range of 41-55 %; however, β-santalol content was close to the specification of 18 %. The total content of bisabolenol A, B, C, D and their isomers was also high i.e. 25.0 % of the oil.[82] In another study, altogether 32 active phytocompounds which were identified in the stem extracts of *Santalum album* by GC-MS study.[83] In a further study, thirty five volatile metabolites were detected by GC-MS analysis from the heartwood of 15 year old tree.[84] Bioassay-guided fractionation of the heartwood of *Santalum album* carried out which led to the isolation of seven α-santalol derivatives including (9R,10E)-9-hydroxy-α-santalal, (10R,11R)-10,11-

dihydroxy-α-santalol, (9E)-11,13-dihydroxy-α-santalol, and (10E)-12-hydroxy-α-santalic acid. Their structures were determined by spectroscopic analysis.[85] HPTLC-based evaluation of sesquiterpenoids from sandalwood oil was developed for profiling of metabolite such as n-alkanes, sesquiterpene, sesquiterpenoids, fatty acids, alcohols and hydrocarbons of sandalwood oil.[23] Srivastava and co-workers studied the functional characterization of novel sesquiterpene syntheses from Indian Sandalwood.[86] Possibility of distinguishing the woods reliably on the basis of anatomical structure, colour of the hot water extract, chemical constituents of oil (mainly santalol content) and DNA fingerprinting was investigated.[87]

The structure-activity relations of odorous compounds from sandalwood were investigated.[88-89] Further, the structure-odour relationship of (*Z*)-α-santalol, the main constituent of sandalwood essential oil having unique woody odour and its derivatives was investigated, focusing on the relationship between the structure of the side chain and the odour of the compounds. The study revealed that odours of the *Z*-isomers were similar to those of the corresponding saturated compounds, but clearly different from the odours of the corresponding *E*-isomers (odourless, fresh, or fatty). These results indicated that the relative configuration of the side chain with respect to the santalane frame plays an important role in the odour of α-santalol. *E*-configuration in the side chain eliminates the woody odour character of α-santalol and its examined derivatives, whereas the *Z*-configuration or saturation of the carbon side chain does not.[90]

Studies on seed and seed oil of Sandal tree,[91] partial hydrogenation of sandal seed oil,[92] removal of unsaponifiables from sandal seed oil, fatty acid composition of seed coat,[93] and compositional changes in seed oil on storage were also reported.[94] Isolation of betulinic acid from sandal seed coat and its reduction of beutlin was reported.[95] Utilization of exhausted sandalwood bark and seeds were explored.[91,96] Arrays of flavonoid constituents vicenin-2, vitexin, isovitexin, orientin, isoorientin, chrysin-8-C-β-D-glucopyranoside, chrysin-6-C-β-D-glucopyranoside and isorhamnetin were isolated and characterized from leaves of *S. album*.[97-98]

The analysis, synthetic substitutes, industrial and therapeutic uses of sandalwood oil was amassed by Ranade.[99] Further, Makoto presented an account of research on natural and synthetic aroma of sandalwood.[100] Synthesis of sandalwood odour derivatives from campholenic aldehyde was reported.[101] A process for synthesis of perfume having alike

flavour was patented that involve oxidation of santalol with MnO_2 in hexane to get Z-α-santalal and its isomerization with 0.5-2% glacial acetic acid to generate the product E-α-santalal.[102] Safety assessment of oil in food products were investigated.[103] Comparative account of the chemical constituents of fragrant sandalwood species, including *S. album*, *S. spicatum* and *S. austrocaledonicum* was studied.[104] Application of a number of essential oil including sandalwood oil in aromatherapy was described by Setzer.[105] Gleason discussed the potential and perspective of using Indian sandalwood oil as raw materials for fine fragrance perfumes.[106] Methods for identification and detection of adulteration were developed.[107-108]

PHARMACOLOGY

Apart from perfumery and cosmetics relevance, sandalwood and its oil have demonstrated a wide range of pharmacological activities. *S. album* has been extensively studied for validation of its traditional therapeutic claims and for revealing further biological efficacies. A number of pharmacological investigations on sandalwood and its oil have reported various biological effects ranging from antibacterial to anticancer. The reported pharmacological activities of sandalwood as well as its oil are summarized hereunder.

Hepatoprotective activity

Hydro-alcoholic extract of the leaves of *S. album* showed significant hepatoprotective activity against CCl_4 and paracetamol induced hepatotoxicity by decreasing the activities of serum marker enzymes, bilirubin and lipid peroxidation and significant increase in the levels of glutathione, superoxide dismutase, catalase and protein in a dose dependent manner, which was further confirmed by the decrease in the total weight of the liver and histopathological examinations.[109]

CNS Effects

Santalum album L. is found to possess memory enhancement potency.[110-111] Studies on sedative effect have shown that inhalation of East Indian sandalwood oil decreased the motility of mice to an extent of 40-78% compared with 0% control.[112] Sedative effect of sandalwood oil and aqueous extract has already been proved.[113-114] Sandalwood oil is reported to have a relaxing effect on the nerves and used for hot or agitated emotional states leading to headaches, insomnia and nervous tensions.[32] Bioactive constituent, Santalols are reported to have central nervous system (CNS) depressant effects hence demonstrate implication in patients having sleep disorders.[115] In a first of its kind study, olfactory

receptor neurons were identified that were specifically stimulated by four synthetic sandalwood compounds and oil.[116] Furthermore, solvent extracts of heartwood were shown to have neuroleptic property in mice. Alpha- and β-santalols significantly increased the levels of homovanillic acid, 3, 4-dihydroxyphenylacetic acid and/or 5-hydroxyindoleacetic acid in the brain of mice upon intra-gastric and intra-cerebro-ventricular routes of administration.[113] Alpha-santalol was shown to be a strong antagonist of dopamine D2 and serotonine 5 HT2A receptor binding. In addition, the effect of alpha-santalol, was the same as that of chlorpromazine as an antipsychotic agent.[117] Alpha-santalol caused significant physiological changes such as relaxing and sedative effects, whereas sandalwood oil provoked physiological deactivation but behavioural activation after transdermal absorption.[118] Recently, TLC_{254} bioautographic assays indicated that alpha-santalol, the major constituent of the oil, is a strong inhibitor of both tyrosinase and cholinesterase *in vitro*, and hence there is a great potential of the essential oil for use in the treatment of Alzheimer's disease as well as in skin-care.[119]

Anti-ulcer Activity

Oral treatment of *S. album* stem hydroalcoholic extract has been reported to demonstrate good level of gastric protection in rats by effectively inhibiting physically (stress) and chemically (both Local Irritant and Drug-NSAID) induced gastric ulceration.[120]

Antibacterial activity

Several studies have focused on the antimicrobial properties of East Indian sandalwood oil[121] while many other studies focused on the Australian sandalwood oil.[122] A comparative study conducted with 26 essential oils screened for antibacterial activities against axilla bacteria demonstrated strongest activities for sandalwood oil and their synthetic analogues.[123] Sandalwood oil is an effective antibacterial agent against Methicillin resistant *Staphylococcus aureus* and antimycotic resistant *Candida* species.[124] Crude extract as well as α- and β-santalol compounds of sandalwood oil exhibit antibacterial activity against *Helicobacter pylori* a Gram-negative bacterium which is strongly linked to the development of duodenal, gastric and stomach ulcers.[26] Sandal wood oil also shows activity against *Herpes simplex* virus Type 1[125] and β-santalol has anti-influenza activity against H3N2 virus. In another study, maximum inhibitory actions of sandalwood oil were recorded against *Bacillus mycoides* and *Escherichia coli*.[126] Methanol extract of *S. album* reported to be effective against *Bacillus subtilis*, *Salmonella typhi*, *Staphylococcus aureus* and

Pseudomonas aeruginosa and highly active against *Candida albicans*.[127] Sandal wood oil showed anti-dermatophytic activity against *Microsporum canis, Trichophyton rubrum* and *Trichophyton mentagrophytes*.[128]

Besides, the sandalwood oil constituents, α-and β-santalol were active against *Salmonella typhimurium* and *Staphylococcus aureus* whereas epi-β-santalene was found to be active against *S. typhimurium*.[128] Santalbic acid (trans-11-octa-decen-9-ynoic acid), a major constituent of the seed, was found to inhibit gram positive bacteria and several pathogenic fungi.[129] Santalols in high and/or medium concentrations found to be active against yeast, gram positive and negative bacteria, showing better antimicrobial efficacy even in low concentrations.[121] Further, immature tree shoots were also shown to be antibacterial against 13 bacterial strains.[130]

Antifungal Activity

Sandalwood oil is reported to possess anti-fungal activity against *Microsporum canis, Trichophyton mentagrophytes* and *T. rubrum*.[131] Sandalwood oil was found to be effective against human pathogenic fungal strains *Microsporum canis*, *Trichophyton mentagrophytes* and *T. rubrum* but was ineffective against *Candida albicans*, *Aspergillus niger* and *A. fumigates*.[132]

Antiviral Activity

The anti-viral activity of sandalwood has also been established through biological studies. Sandalwood oil has been shown to be used in prevention and treatment of warts, skin blemishes and other viral induced tumours on skin.[133-134] Traditional medicine system including Ayurvedic and Chinese medicine also mention about the antiviral potency sandalwood oil.[135] In an *in vitro* study, sandalwood oil demonstrated antiviral activity against *Herpes simplex* viruses (HSV)-1 & 2 in a dose-dependent manner through inhibition of viral replication. It was further assumed that sandalwood oil helped protect the cells by modulating liver's gluthatione, S-transferase and levels of acid-soluble sulfhydryl.[136] Sandalwood oil showed *in vitro* inhibitory effect against herpes simplex virus type 2 (HSV-2) on RC-37 cells. Interestingly, sandalwood oil only affected the virus before adsorption into the cells by some non-specific inhibition of interaction between the virus and host cells.[25] Sandalwood oil constituents, α- and β-santalols, their mixtures and derivatives have been implicated in treatment of warts in human, especially HPV and DNA pox virus that causes

Molluscum contagiosum and speculated to be a cure against HIV and other RNA viruses, as well as dryness, flakiness and dryness associated with seborrheaic dermatitis, psoriasis and allergic or eczematous rashes of the skin as well as in the treatment of acne lesions of the face and the body and in the eradication of pustular acne lesions caused by staphylococcal acne and streptococcal bacterial infections. Additionally, sandalwood oil and santalol derivatives claimed for use in treating cold sores and herpes.[137] Recently, single cell and somatic embryo suspension cultures of Indian sandalwood tree is demonstrated as the alternative and renewable resource of shikimic acid, the precursor for industrial-scale synthesis of Tamiflu, the sole commercially available neuraminidase inhibitor drug against Influenza A virus.[138]

Antioxidant efficacy

The phytochemical and pharmacological investigations proved the presence of antioxidant principles that justify their traditional medicinal values.[139] *S. album* and other Indian medicinal plants were tested *in-vitro* for their possible regulatory effect on nitric oxide (NO) levels using sodium nitroprusside as NO donor. Most of the plant extracts demonstrated significant direct dose dependant scavenging activity on NO.[140] It has been reported to have nitrous oxide scavenging activity and DPPH antioxidant activity.[140,141] *Santalum album* can protect cardiac tissue from oxidative stress induced cell injury and lipid peroxidation and also interferes with DOX-induced inflammatory and apoptotic induction in cardiac tissue.[142]

Recently, an anthocyanic pigment cyanidin-3-glucoside from *S. album* was shown to be antioxidant and nutritionally important.[143] Additionally, in a comparative study it was shown that *in vitro* grown callus cells demonstrated comparable antioxidant activities with sandalwood oil, using nine *in vitro* antioxidant tests.[144] Sandalwood oil increased glutathione S-transferase (GST) activity and acid soluble sulfhydryl (SH) levels in the liver of adult male Swiss albino mice.[145] Enhanced GST activity and acid-soluble SH levels were suggestive of a possible chemopreventive action of sandalwood oil on carcinogenesis through a blocking mechanism. Similarly, methanolic extracts of sandalwood demonstrated acetyl cholinesterase inhibitory and DPPH and super oxide free radical scavenging activities in albino mice, there by indicating potential to tackle dementia and memory loss, associated with Alzheimer's disease. Recently, anti-hyperglycemic and antioxidant potential of sandalwood oil and its major constituent α-santalol in alloxan- and D-galactose mediated oxidative stress induced diabetic male Swiss albino mice models has been demonstrated in an *in vivo* study.[146]

Haemolytic activity

Haemolytic activity of any compounds is an indicator of general cytotoxicity towards normal healthy cells.[147] In a study, it was found that leaf extract of the plant produced the lyses of RBC. However, this haemolytic activity only takes place with parenteral administration. The study revealed that the leaves of the plant contained saponins responsible for haemolytic activities against blood.[148]

Anticancer activity

Investigations have shown the chemo-preventive effects and molecular mechanisms of α-santalol on skin cancer development in both animal models and skin cancer cell lines.[149] Anticancer effects of oil has been reported in chemically-induced skin carcinogenesis in CD-1 and SENCAR mice, ultraviolet-B-induced skin carcinogenesis in SKH-1 mice and *in vitro* models of melanoma, non-melanoma, breast and prostate cancer and its ability to induce cell-cycle arrest and apoptosis in cancer cells has also been demonstrated.[150] Sandalwood oil constituent, α-santalol delayed the papilloma development in both strains of mice.[151] Alpha-santalol at a concentration of 25-75 μM has been found to induce apoptotic death of human epidermal carcinoma A431 cells via caspase activation together with loss of mitochondrial potential and cytochrome release.[152] In a similar study, in female hairless mice strain SKH-1, topical application of α-santalol demonstrated chemopreventive effects as observed from reduced ornithine decarboxylase activity, tumour incidence, and multiplicity.[153] Moreover, α-santalol was shown to delay skin tumour development, reduced tumour multiplicity, inhibited *in vitro* lipid peroxidation in skin and liver microsomes and hence prevented UVB-induced skin tumour development possibly by acting as an antiperoxidant.[154] Alpha-santalol reported to increase significantly apoptosis related proteins, caspases 3 and 8 levels and tumour suppressor protein p53, via an extrinsic pathway in UV B induced skin tumour development model in SKH-1 mice.[155] In human prostate cancer cells, α-santalol induced apoptosis by causing caspases-3 activation.[156] About six novel sesquiterpenoids, two aromatic glycosides and several neolignans were identified from sandalwood heartwood chips, which were evaluated for *in vitro* Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells, for assessing antitumor promoting activity. Further, *in vivo* two-stage carcinogenesis assays demonstrated its potent inhibitory effect on EBV-EA activation strong suppressive effect on two-stage carcinogenesis on mouse skin.[157] Moreover, derivatives of α-santalol demonstrated tumour-selective cytotoxicity in HL-60 human promyelocytic

leukemia cells and TIG-3 normal human diploid fibroblasts.[158] Two lignans obtained from the heartwood samples, demonstrated apoptosis induced tumour cell cytotoxicity against HL-60 human promyelocytic leukemia cells and A549 human lung adenocarcinoma cells.[27] α-Santalol, an active component of sandalwood essential oil has been studied for skin cancer preventive efficacy in murine models of skin carcinogenesis.[159]

Antipyretic activity

The sandalwood oil at a dose of 200 mg/kg showed highly significant antipyretic effect against yeast induced pyrexia in albino rats.[8]

Antiinflammatory activity

Santalols have been reported to possess a significant anti-inflammatory property, in several experimental models.[33] *Santalum album* possessed anti-inflammatory and antiulcer activities as evidenced by its significant inhibition in the carrageenan induced paw edema, cotton pellet induced granuloma, as well as pylorus ligation induced ulcer. These findings could substantiate the inclusion of this plant in the effective management of inflammatory disorders like ulcer in traditional system of medicine. The *in vitro* antioxidant (and *in vivo* analgesic and antiinflammatory activities in mice were established for methanolic extracts of heartwood.[160]

Antihyperglycemic and antihyperlipidemic effect

Studies on antihyperglycemic and antihyperlipidemic effect of long-term oral administration of petroleum ether fraction of sandalwood in streptozotocin induced diabetic rats showed reduction in blood glucose level. Metformin treated group also showed a decrease in blood glucose as against an increase in diabetic control group. Further, total cholesterol (TC), low density lipoprotein (LDL) and triglyceride (TG) levels were decreased in treated diabetic rats whereas, cardioprotective, high density lipoprotein (HDL) were increased. Significant improvement in atherogenic index was observed that led to the conclusion that *S. album* has potential antihyperglycemic and antihyperlipidemic activities.[161]

Cardioprotective activity

Aqueous extract of sandalwood reported to inhibit significantly the cardiac tissue damage by reducing lipid peroxidation on doxorubicin induced cardiotoxicity in rat model[162] and significant protective effect against ISO induced myocardial infarction in albino Wistar rats in dose dependant manner.

Physiological effects

Sandalwood oil and its major constituent, α-santalol are found to affect several physiological functions and sensory stimulation. The oil reported to elevate pulse rate, skin conductance level and systolic blood pressure whereas α-santalol elicited higher ratings of attentiveness and mood than the oil.[163] Inhalation of sandalwood oil reported to improve audibility.[164] Recently, sandalwood tea was demonstrated to increase significantly the myocardial contractility and heart rate of the isolated and failed frog heart, while it showed good effect as anti-fatigue in contracting the smooth muscle of isolated rabbit aortic strips.[165] Sandalwood oil did not demonstrate any phototoxic effects though occasional cases of irritation or sensitization reactions in humans are reported.[166]

Metabolic effects

Sandalwood oil reported to demonstrate changes in neonatal hepatic xenobiotic metabolizing enzymes in suckling mouse pups on trans-mammary exposure. It is further observed that sandalwood oil and its constituents passed through milk and modified the hepatic xenobiotic metabolizing enzymes such as increased hepatic glutathione-S-transferase, glutathione reductase and glutathione peroxidase activities, with concomitant increase in hepatic cytochrome b5 and acid soluble sulfhydryl contents and lowering of hepatic cytochrome P 450 content.[167]

Genotoxicity effects

The DNA damaging activity of sandalwood oil in *Bacillus subtilis* was studied and was found to be non-genotoxic.[168] Similarly, sandalwood oil-induced inhibition of *B. subtilis* showed it to be non-genotoxic.[169]

Genitourinary system effects

Genitourinary tract infections such as cystitis and gonorrhea have been treated by sandalwood oil for years owing to the astringent properties of the oil and its effect on the mucus membranes of genitourinary tract; helps remove mucous congestion, restore mucous membrane and minimize the risk of infections such as herpes virus.[170] These traditional uses make sandalwood oil suitable for anti-ageing skin care, for toning effects and to prevent skin from ugly scars in modern cosmeceutical applications.

Insecticidal activities

Sandalwood oil acts as a repellent against *Varroa jacobsoni* [171] in honey bee colonies thus used as an acaricide. A modest activity against *Lycoriella mali* (the mushroom fly) is also reported.[172] The oil was also found to be impenetrable to termites.[173] Owing to its acaricidal and oviposition deterring effects, santalol is found to be active against spider mites *Tetranychus urticae***.**[174-176]

Dietary aspects

Sandalwood oil is considered safe as a flavouring ingredient with a daily consumption 0.0074 mg/kg and has a long history of oral use as dietary supplements without any reported adverse effects.[166] Sandalwood oil was shown to have inhibitory action on hyperactive small intestine movement in mice, thereby showing antagonistic action on intestinal spasm caused by acetylcholine, histamine and barium chloride.[177] Furthermore, it was recently shown that leaf extracts of sandalwood tree demonstrated antihyperglycemic and antihyperlipidemic effects in streptozotocin induced diabetic rats.[161]

Aromatherapy

Sandalwood oil is relaxing, soothing, cooling, sensual and valued for its own sweet, warm, rich balsamic aroma. It is an excellent addition to massage and facial oils, bath oils, aftershaves, lotions and creams. It blends especially well with floral or other oils dominated by their top or middle notes, but works with almost any oil providing or enhancing the base note and lending its fixative ability. It is suited for both feminine and masculine formulas. It is suitable for all skin types and is especially useful for chapped, dry, sensitive or inflamed skin. It promotes restful sleep and helps to ease an anxious mind. It is grounding in times of emotional distraction and helps bring peace and acceptance in times of loss. Sandalwood oil can be used in modern aromatherapy for treating several conditions. Due to its emollient properties, Sandalwood is very much used for skin care. The oil has a relaxing effect on the nerves and may be used for hot, agitated emotional states leading to conditions such as headaches, insomnia and nervous tension. It can be used in cases of respiratory tract infections, chronic bronchitis involving a chronic dry cough, especially when its soothing, demulcent effects are required.[20-22,35] Sandalwood is an astringent and helps to resolve mucous congestion. Sandalwood oil helps to restore the mucous membrane and minimise the risk of infection.[32] Has been used for years for genitourinary tract infections e.g. Cystitis and gonorrhoea. When applied to the skin, sandalwood oil is soothing, cooling and moisturising

and primarily used for dry skin conditions caused by loss of moisture and skin inflammations. It may be used to relieve eczema and psoriasis and for the treatment of oily skin and acne. There are two major modes of administer including topical application (e.g. massage, compress, bath, sitz bath, douche, ointment, skin care, etc) and inhalation (e.g. direct inhalation, diffuser, oil, vaporiser and steam inhalation.[32]

RESEARCH PROSPECTS

Phytochemical research has led to the isolation and characterization of an impressive number of biologically active chemical constituents from sandalwood and its oil.[178] Yet, possibilities are there for finding novel chemical entities. Pharmacological investigation have not only validated the traditional medicinal practices but also discovered several new therapeutic potential of sandalwood and its constituents.[179] *S. album* oil has been used in preparation of Chinese medicine for treating coronary heart disease,[180] depression and bone fracture,[181] poliosis,[182] schizophrenia,[183] alcoholic hepatitis,[184] controlling blood sugar without risk of hypoglycaemia[185] and development of various cosmetic products.[186]

Recent pharmacological and clinical studies have found sandalwood constituents to demonstrate mammalian DNA polymerase-inhibitory, cancer cell growth inhibitory, antiallergic, and anti-β-hexosaminidase release activity and antioxidant activity.[187] Most of the biological activities have been attributed to the sesquiterpenoids constituents including α- and β-santalenes and santalols. Now it has been made possible to clone and characterize a number of genes and encoded enzymes responsible for santalene biosynthesis.[188] This accomplishment has directed towards the possibility for better understanding of the biosynthetic routes, phytochemical diversity of bioactive santalols through genetic approach. Also, the microbial metabolic engineering approaches paved the path to obtain diversity of sandalwood sesquiterpenoids in desirable quantities for flavour and fragrance industry.[189] With escalating global demands, biotechnological means may facilitate productivity enhancement of Sandalwood resource and bioactive constituents. Furthermore, bioinformatics approaches and softwares have been developed for prediction and detection of natural products from genomic sequences to facilitate industrial high-throughput screening in drug discovery.[190] Recent improved analytical tools and techniques including precision chromatography systems (like MDGC, GC-MS)[191] and spectroscopic techniques for quality control[192-193] have facilitated addressing the complex research and analytical needs. Furthermore, it has been recently stressed that Ayurvedic wisdom, traditional documented

use, tribal non-documented use and exhaustive literature search should be applied to synergize efforts in drug discovery from plant sources and identification of appropriate candidate plants.[194] With global upsurge in interest for plant derived products owing to adverse side effects of their synthetic counterparts, researchers are striving hard to develop new efficacious pharmaceutical, nutraceutical and cosmeceuticals of plant origin deriving clues from the treasure of traditional and ehthnobotanical knowledge Research endeavours are not confine only to isolation and characterization of new molecular entities but also scientific validation of traditional herbal formulations with strong scientific evidence. A number age old therapeutic applications of sandalwood and its essential oil are yet to be scientifically validated, which provides opportunity for chemo-biological research and clinical studies.

Global sandalwood resources are diminishing and the demand is increasing.[195] The natural population of Sandalwood tree is alarmingly threatened by mycoplasmal spike disease, illegal poaching and over exploitation to meet the rising global demands that have resulted in the tree being inducted into International Union for Conservation of Nature (IUCN) Red List of Threatened Species as vulnerable.[196] Hence, *in vitro* micropropagation in the form of callusing, somatic embryogenesis, regeneration protocols, somatic embryo production[197] possessing greater accumulation of sandalwood oil constituents[198] may provided immense scopes for biotechnological means of conservation of the species.

CONCLUSION

Santalum album is one of the most famous and widely used plants in perfumery and cosmetics. Apart from perfumery and cosmetics uses, sandalwood also has a wide range of pharmacological activities and the plant can be considered as one of the important medicinal plants. Since last two decades, this plant has been studied extensively but still there is lot of scope to exploit full potential of uses of sandalwood for mankind. Researchers across the globe have been focussing on the study of interesting chemical constituents especially sesquiterpenoids of sandalwood for more than a century with regard to their structure, , synthesis and pharmacological effectiveness. With recent upsurge in research endeavours to verify the traditional healthcare uses of essential oil and their constituents by modern experimental approaches that have provided momentum to in depth pharmacological and mechanistic investigations. Various studies have established the versatile pharmacological effectiveness of sandalwood and its oil ranging from antibacterial to anticancer. It also shows

prominent activity in various skin diseases. There are few toxicological studies on sandalwood. It is necessary to summaries all activities reported about this plant. This review consolidates different reported activities of sandalwood plant as well as its oil.

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