

***Santalum album* Linn wood and its oil: An aromatic Unani traditional medicine with versatile pharmacological activities**

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ABSTRACT

Santalum album Linn. [Family: Santalaceae] is commonly known as white sandalwood, *sandal safaid* and *safed chandan*. It is one of the most valuable trees and second costliest wood in the world. Sandalwood and its oil is extensively used in the Unani and other traditional systems of medicine as it has blood purifier, anti-inflammatory, analgesic, exhilarant, cardiogenic, antiseptic, nervine tonic and expectorant properties. It is used in skin, cardiac, liver, gastrointestinal, respiratory, integument and urogenital disorders. These uses are supported and proven by many *in vitro* or *in vivo* studies. The proven pharmacological activities of *S. album* are antimicrobial, anti-oxidant, anti-inflammatory, antimutagenic and anti-fatigue. The research has proven that sandal oil or its constituents have anti-microbial activity. Sandalwood oil showed skin cancer preventive effect in mice and its constituent alpha santalol showed the anticancer property. The methanolic extract of wood was confirmed for antioxidant, free radical scavenging, analgesic and anti-inflammatory activities. α and β santalols present in sandal oil showed sedative effects. Sandalwood tea had a significant effect on heart muscles of frog and showed increased myocardial contractility. Its oil showed significant changes in hepatic xenobiotic metabolizing enzymes. Sandalwood oil and its major constituents showed less acute oral and dermal toxicity in laboratory animals. Hence, the aforementioned studies justify the uses of sandalwood and its oil mentioned in the classical Unani literature. However, further clinical trials are suggested to confirm its efficacy and safety in humans.

Keywords Antioxidant, Cardiogenic, *Santalum album* Linn, Santalol, Unani system of medicine

INTRODUCTION

One of the famous Traditional systems of medicine is the Unani system of medicine since antiquity. This medicine is based on the philosophy of the Greek physicians Hippocrates and Galen that subsist and preserves its traditional fundamental nature till date (Sultana et al., 2015). Presently thousands of texts/manuscripts of Unani traditional literature are available for practice worldwide.

The reliable sources/texts of Traditional Unani medicine have described regarding the plant, *Santalum album* Linn. For this reason, comprehensive literature search to appraise the description of the *Santalum album* wood and its oil discussed in traditional Unani literature was comprehended. The Traditional Unani texts viz., Hamdard Pharmacopoeia of Eastern Medicine, Al Qanoon fit Tibb (Canon of Medicine), Khazainul Advia, Makhzan al-Mufradat, Unani Pharmacopoeia of India, Jamia ul Mufradat al Advia al Aghiza, Busthan al-Mufradat, Wealth of India and Indian Medicinal plants were explored. These traditional manuscripts/texts were searched for the Unani morphology, the traditional pharmacological actions, uses and

compound formulations. Additionally, browsing of Google Scholar/PubMed/Medline and other search engines was explored for ethnobotanical description, phytoconstituents, and pharmacological activities.

Introduction of plant

Santalum album Linn. [Family: Santalaceae] is a small to medium-size hemiparasitic tree, commonly known as white sandalwood (English), *safed chandan* (Hindi), *sandal safaid* (Urdu) etc. It is one of the most valuable trees and second costliest wood in the world. Sandalwood is very much prized in Hindu mythology. According to Vamana Purana, the wood is recommended for worshipping God Shiva. Goddess Lakshmi is believed to reside in the sandalwood tree. In Buddhism, it is considered to be one of the three incenses integral to Buddhist practice, together with Aloes wood and Cloves. The ancient Egyptians imported the sandalwood and used it in medicine, for embalming the dead and in the ritual burning to worship the gods (Kumar et al., 2012).

Sandalwood is extensively used as a fragrance ingredient in soaps, detergents, creams, lotions, perfumes, etc. It is also employed as flavouring agent in many food products. Sandalwood and its oil have been widely used in the Unani system of medicine since ancient time. Pedanius Dioscorides who lived in first century AD was a Greek botanist and physician. He authored *De Materia Medica* an encyclopaedia in Greek on medicinal plants which was the source for all modern pharmacopoeias. It consists of five volumes and discussed about 600 plants. Sandalwood was recorded by Dioscorides in De

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Received Aug 09, 2018; Accepted Aug 16, 2018; Published Aug 31, 2018

doi: <http://dx.doi.org/10.5667/tang.2018.0016>

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Materia Medica, since then it is continuously mentioned in all alternative system of medicine. In the Unani system of medicine, it is useful to treat skin, cardiac, liver and gastrointestinal, respiratory disorders, integument and locomotors diseases (Ghani, 2004). In folk medicine, it is in use to treat common colds, bronchitis, skin disorders, heart ailments, general weakness, fever, infection of the urinary tract, inflammation of the mouth and pharynx, liver and gallbladder complaints and other maladies (Nadkarni, 2009). These uses in the Unani and other Traditional systems of medicine is supported and proved by many research works.

Vernacular Name

English: Sandal tree, white sandal

Hindi: *Safed chandan, santal*

Kannada: *Bavanna, srigandadamara, agarugandha*

Malayalam: *Candanam*

Sanskrit: *Candanah, srikhandam*

Tamil: *Andanam*

Telugu: *Candanamu, gandhapucekka, srigandapumanu, tellagandhapucettu.*

Unani: Sandal-e-safaid (Khare, 2007)

Habitat

The natural distribution of sandalwood extends from 30°N to 40°S from Indonesia in the East to Juan Fernandez Islands (Chile) in the West and from Hawaiian Archipelago in the North to New Zealand in the South. It is distributed widely in India especially in the southern region, e.g., Karnataka, Tamil Nadu and Kerala (Kumar et al., 2012). However, disagreement persists as to whether it is native to India or was introduced for cultivation over 2000 years ago from Indonesia (Harbaugh and Baldwin, 2007) or Australia.

Description

It is a medium-sized evergreen, hemiparasitic, glabrous tree, with slender drooping branches, reaching up to 18 m in height. The bark is dark grey or brownish black, rough with short vertical cracks. The leaves are simple, opposite elliptical, lenceolate, glabrous and entire. The flowers are brownish purple, reddish purple, or violate, axillary and paniculate cymes. The fruits are globose drupes, purple-black with ribbed endocarp and seeds are hard and globose. The heartwood is light yellowish brown when fresh and turns dark brown to dark reddish brown on exposure. The wood is highly scented (Prajapati et al., 2003).

Pharmacological actions in the Unani system of medicine

Sandalwood powder and its oil are categorized as cool and dry according to the temperamental theory. It is useful in the most of hot and wet ailments. It is used as *muqawwie qalb* (cardio-tonic), *muhaferrah* (exhilarant), *muqawwie dimagh* (nervine tonic), *munaffise balgham* (expectorant), *muqawwie meda* (gastro-protective), *qabiz amaa* (constipative), *mudir baul* (diuretic), *dafe taffun* (antiseptic), *musaffi khoon* (blood purifier), *musakkin alam* (analgesic), *muhallil* warm (anti-inflammatory) etc. The sandalwood powder or its oil is used by oral route or applied externally in the form of paste (Ghani, 2004; Baitar 1999).

The above mentioned uses as per the Unani texts are supported and confirmed by many in-vitro, in-vivo, experimental and clinical works.

Ethnopharmacological activities

Sandal wood has diaphoretic, cooling, expectorant, diuretic, antiseptic and bacteriostatic against Gram positive bacteria. It is

used in chronic cystitis as it has urinary antiseptic property. It is also useful for sexually transmitted diseases. During fever, its paste is applied to one's temples for headache. The paste is also applied for local inflammations, burns and skin diseases to allay pruritus (Khare, 2007).

Contraindication

Sandal wood is contraindicated in the diseases of the parenchyma of the kidney (Khare, 2007).

Chemical constituents

The volatile oil extracted from *Santalum album* derived from the roots and heartwood is colourless to yellowish, viscous liquid (ref. index-1.499-1.506, specific gravity 0.962-0.985 opt, rotation -19-20o) with peculiar heavy sweet odour. The chief constituents of the oil is santalol (90% or more), which is a mixture of two primary sesquiterpene alcohols (C₁₅H₂₄O) viz., α -santalol (bp-166-167oC) and β -santalol (bp-177-178oC). Alpha form is more predominately present in the sandalwood oil.

More than hundred constituents of sandalwood oil in categories of tannins, terpenes, resins, and waxes have been reported. These include such as hydrocarbons- santene (C₉H₁₄), nortricyclo-ekasantalene (C₁₁H₁₈), α - and β -santalenes (C₁₅H₂₄), alcohols-santenol (C₉H₁₆O), teresantalol (C₁₀H₁₆O), aldehydes- nor-tricyclo-kasantalal (C₁₁H₁₆O) and the acids α -and β -santalal acids, (C₁₅H₂₂O₂) and teresantalal acids (C₁₀H₁₄O₂) (Sindhu et al., 2010).

Pharmacological activities

Analgesic and anti-inflammatory activity

Saneja et al., (2009) evaluated the methanolic extract of wood for analgesic and anti-inflammatory activities at various doses. The analgesic and anti-inflammatory effect of extract was compared with diclofenac sodium (7 mg/kg) as the standard. The maximum effect of the extract was seen at 500 mg/kg.

Antimicrobial activities

The antibacterial properties of the five different extracts of sandalwood and sandalwood oil were evaluated. The extracts were screened against nine Gram-negative and five Gram-positive bacterial strains by disc diffusion, agar spot, and TLC bio-autography methods. The minimum inhibitory concentration (MIC) for sandalwood oil was determined to be in the range of 0.078-5 μ g ml⁻¹ for most of the test micro-organisms screened. Among the different extracts screened, the somatic embryo extracts showed the strongest antibacterial activity (Misra and Dey, 2012).

Jirovetz et al., (2006) evaluated the antimicrobial activities against the yeast *C. albicans*, the Gram-positive bacterium *S. aureus* and the Gram-negative bacteria *E. coli*, *P. aeruginosa* and *K. pneumonia*. An agar dilution and agar diffusion method was used to study antimicrobial activity in eight different samples of sandalwoods, a mixture of α - and β -santalols. Eugenol was taken as reference compound. They conclude that santalols in medium and/or high concentrations in sandalwood oils have a significant antimicrobial potential.

Ashok and Ayaprakash (2012) in their study evaluated the antibacterial activity against the bacterial species including *B. subtilis*, *S. aureus*, *E. coli*, *S. typhi*, *K. pneumonia* and *P. aeruginosa*. They also studied the antifungal activity in fungal species, *A. niger* and *A. fumigates*. The results revealed moderate zone of inhibition against *S. aureus*, *E. coli*, *K. pneumonia* and *A. niger*. No inhibitory effect was found against *A. fumigates*, *S. typhi*, *P. aeruginosa* and *B. subtilis*. The

highest activity was found against *K. pneumonia* and *A. niger*. The lowest activity was found against *S. aureus*.

Patil et al., (2011) found that *S. album* alcoholic seed extract at a concentration of 5 mg/ml did not showed any zone of inhibition against gram-positive bacteria *B. subtilis* and *S. aureus* and gram-negative *E. Coli*, *P. aeruginosa* and fungus *C. albicans*.

Ochi et al. (2005) isolated six new sesquiterpenes from *S. album* and they assessed anti-*Helicobacter pylori* effect. They concluded that the crude extracts and the isolated compounds showed antibacterial activity against *H. pylori*. Further, they noted that especially, compounds 7 and 8 showed strong anti-*H. pylori* activities against a clarithromycin-resistant strain as well as other strains.

Antioxidant activities

The effect of *S. album* wood oil on glutathione S-transferase (GST) activity and acid soluble sulphhydryl (SH) levels in the liver of adult male Swiss albino mice was studied. The oil showed enhanced GST activity and acid-soluble SH levels, which was suggestive of a possible chemopreventive action (Banerjee et al., 1993). Saneja et al., (2009) found the *in-vitro* antioxidant activity of methanolic extracts of heartwood of Sandal at 100-500 mg L⁻¹ in mice. The dichloromethane-methanol extract of *in-vitro* grown callus cultures of *S. album* L. showed antioxidant activity in ferric reducing assay power, total antioxidant capacity, metal ion chelation, inhibition of lipid peroxidation and in scavenging of hydroxyl radical, 2, 2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid, di (phenyl) (2, 4, 6-trinitrophenyl) imaginazium (DPPH.) and nitric oxide free radical scavenging and reducing power assays that was comparable to antioxidants such as quercetin, gallic acid and α -tocopherol (Misra and Dey, 2012). Intraperitoneal administration of α -santalol 100 mg/kg BW and sandalwood oil 1 g/kg BW for a week modulated parameters such as body weight, blood glucose, serum bilirubin, liver glycogen, and lipid peroxides contents to normoglycemic levels in alloxan-induced diabetic male Swiss albino mice models (Misra and Dey, 2013). Harsha et al., (2013) identified a major pigment cyanidin-3-glucoside from berries *S. album*. Further, they evaluated its reducing power and DPPH scavenging assays. They concluded that said molecule has the highest antioxidant activity in methanol and extract also efficiently protected bleaching of β -carotene in β -carotene-linoleate model.

Antihyperglycemic and antihyperlipidemic effect

The long-term oral administration of the *S. album* pet ether fraction in streptozotocin-induced diabetic rats demonstrated reduction in blood glucose, total cholesterol, low-density lipoprotein and triglyceride levels. However, high-density lipoprotein was increased. A significant improvement in the atherogenic index was also observed in treated rats (Kulkarni et al., 2012). It was observed that sandalwood seed oil also modified the fatty acid composition of mouse adipose tissue, brain, and liver (Liu and Lomgmore, 1997). Further Li et al., (2013) evaluated the effect of sandalwood seed oil on fatty acid (FA) profiles and inflammatory factors in male Sprague-Dawley rats. The rats were fed on soybean oil, olive oil, safflower oil, linseed oil and sandalwood oil. The sandalwood seed oil group showed a higher total n-3 polyunsaturated fatty acids (PUFA) levels but lower n-6:n-3 PUFA ratios in both adipose tissue and liver. Their study suggested that sandalwood seed oil could increase tissue levels of n-3 PUFA, DHA and reduce the n-6:n-3 ratio. It also showed increased anti-inflammatory activity in rats.

Antiviral activity

Sandalwood oil was tested for *in-vitro* antiviral activity against Herpes simplex viruses-1 and -2. It was found that dose-dependent inhibition in replication of viruses in presence of the oil. However, the oil was not virucidal and showed no cytotoxicity effect (Benencia and Courreges, 1999).

Essential oils from sandalwood were screened by Koch et al. (2008) for its inhibitory effect against Herpes simplex virus type 2 (HSV-2) *in-vitro* on RC-37 cells using a plaque reduction assay. The inhibitory concentration (IC₅₀) was determined at 0.0015% for sandalwood oil. The results clearly showed dose-dependent effect of sandalwood oil. In order to determine the mode of the inhibitory effect, essential oils were added at different stages during the viral infection cycle. However, no inhibitory effect could be observed when the essential oils were added to the cells prior to infection with HSV-2 or after the adsorption period. These results indicate that essential oils affected HSV-2 mainly before adsorption probably by interacting with the viral envelope.

Effect on central nervous system

Ohmori et al., (2007) investigated the effect of santalol on the sleep-wake cycle in sleep-disturbed rats. When inhaled at a concentration of 5 X 10⁽⁻²⁾ ppm, santalol caused a significant decrease in total waking time and increase in total non-rapid eye movement (NREM) sleep time. They confirm that santalol act via the circulatory system rather than the olfactory system. It was absorbed in the blood through the respiratory mucosa and exerts its action.

Further, Hongratanaworakit et al., (2004) evaluated the effect of sandalwood oil and alpha-santalol on physiological parameters, mental and emotional conditions in healthy human volunteers after transdermal absorption. They have noted eight physiological parameters i.e., blood oxygen saturation, blood pressure, breathing rate, eye-blink rate, pulse rate, skin conductance, skin temperature, surface electromyogram and subjective mental and emotional condition. They concluded that alpha-santalol caused significant physiological changes, which were interpreted in terms of a relaxing/sedative effect. Furthermore, sandalwood oil also provoked physiological deactivation. In another study, Heuberger et al., (2006) investigated the effects of inhalation of East Indian Sandalwood essential oil alpha-santalol, on human physiological parameters and self-ratings of arousal (alertness, attentiveness, calmness, mood, relaxation and vigor) in healthy volunteers. In comparison to either an odorless placebo or alpha-santalol, Sandalwood oil elevated pulse rate, skin conductance level, and systolic blood pressure. Alpha-santalol, however, elicited higher ratings of attentiveness and mood than did Sandalwood oil or the placebo. The analysis revealed that these effects were mainly due to perceived odor quality. The results suggested a relation between differences in perceived odor quality and differences in arousal level.

Okugawa et al., (1995) evaluated the effect of benzene, chloroform, methanol and water extract on the central nervous system of mice following intra-peritoneal administration. They noted potentiating of hexobarbital sleeping time, body temperature alterations, anti-nociceptive and spontaneous motor activity changes. They found that the benzene extract was most active. The α - and β -santalols were isolated from the active fraction. They were both active by the intragastric and intracerebroventricular routes of administration. They concluded that α - and β -santalols contribute to the sedative effect of sandalwood. Additionally, they found that α - and β -santalols significantly increased the levels of homovanillic acid, 3, 4-dihydroxyphenylacetic acid and/or 5-hydroxyindoleacetic

acid in the brain of mice and worked as a neuroleptic by the resemblance to the pharmacological activities of chlorpromazine. They also evaluated the effect of α - and β -santalols on opioid receptors. They noticed that the inhibitory activities of α -santalol on opioid receptors were only by the δ antagonist, not by the μ - or κ -antagonists and mechanism was different from that of morphine. The α -Santalol also showed to be the potent antagonist of dopamine D2 and Serotonin S-HT2A receptor binding (Okugawa et al., 2002).

Effect on the cardiovascular system

The ethanol sediments prepared with water decoction of sandalwood tea was evaluated for the effect on myocardial contractility and heart rate using the isolated frog heart by the Straub method. The role of sandalwood tea on anti-myocardial hypoxia by tracheal ligation in mice, the influence of sandalwood tea on vasomotor by isolated rabbit aortic strips and anti-fatigue/stress function in swimming rats were evaluated. The results showed that sandalwood tea significantly increased the myocardial contractility and heart rate of the isolated and failed frog heart. No significant improvement was noted on the normobaric hypoxia tolerance of rats (Qin et al., 2010).

Anticancer effects

Dwivedi et al., (2003) showed that α -santalol delayed the papilloma development in skin cancer on CD-1 and SENCAR mice, in which carcinogenesis was initiated with 7, 12-dimethylbenz (α) anthracene (DMBA) and promoted with 12-O-tetradecanoylphorbol-13-acetate (TPA).

Further, Kaur et al., (2005) confirmed that alpha santalol induces the apoptotic death of human epidermal carcinoma A431 cells at a concentration of 25-75 μ M, via caspase activation in both dependent and independent manner with loss of mitochondrial potential and cytochrome release.

In another study topical application of α -santalol (5 mg mL⁻¹) in female hairless mice strain SKH-1 showed reduced ornithine decarboxylase activity, tumor incidence, and multiplicity in tumorigenesis cases induced by means of UV-B irradiation alone, UV-B irradiation along with DMBA or UV-B irradiation along with TPA.

Bommareddy et al., (2007) evaluated the lowest effective concentration of santalol for the chemopreventive effects on UVB-induced skin tumor development in mice and determined antiperoxidant effect of alpha-santalol in order to elucidate its possible mechanism of action. They found that the application of alpha santalol (5%) significantly delayed skin tumor development, reduced tumor multiplicity and inhibited *in-vitro* lipid peroxidation in skin and liver microsomes. They concluded that alpha santalol application prevents UVB-induced skin tumor development possibly by acting as an antiperoxidant. In continuation to this study, further, alpha-santalol was evaluated for its possible mechanism of action and found that alpha-santalol (5 mg mL⁻¹) significantly increased the apoptosis related proteins, caspases 3 and 8 levels and tumor suppressor protein p53, via an extrinsic pathway in SKH-1 mice where skin tumor was developed through UV B (Arsada et al., 2008).

Bommareddy et al., (2012) found that α -santalol induces apoptosis in human prostate cancer cells by causing caspases-3 activation. Six sesquiterpenoids, glycosides and several neolignans identified from sandalwood demonstrated their potent inhibitory effect on in-vitro Epstein-Barr virus early antigen activation in Raji cells (for assessing antitumor promoting activity) and in-vivo two-stage carcinogenesis assays Epstein-Barr virus early antigen activation, and also

strongly suppressed two-stage carcinogenesis on mouse skin (Kim et al., 2006). Matsuo and Mimaki identified two lignans from the heartwood samples and confirmed its apoptosis induced tumor cell cytotoxicity against HL-60 human promyelocytic leukemia cells and A549 human lung adenocarcinoma cells (Matsuo and Mimake, 2010). Further, they studied the derivatives of α -santalol that demonstrated tumor-selective cytotoxicity in HL-60 human promyelocytic leukemia cells and TIG-3 normal human diploid fibroblasts (Matsuo and Mimake, 2012).

Effect on gastrointestinal tract

The hydroalcoholic extract of *Santalum album* showed significant increase in healing of ethanol, indomethacin and stress induced chronic gastric ulcer in rats (Ahmed et al., 2013). Sandalwood essential oil showed an inhibitory effect on the spontaneous movement of guinea pig isolated ileum and an antagonistic action on intestinal spasm caused by acetylcholine, histamine and barium chloride. Oil also had a significant antagonistic effect on small intestinal movement in neostigmine treated mice (Jian-sheng et al., 2010).

CONCLUSION

The Sandalwood and its oil are in use since ancient times for fragrance as well as for the treatment of various diseases. Traditionally, it has cardiogenic, exhilarant, nervine tonic, expectorant, gastroprotective, diuretic, antiseptic, blood purifier, analgesic, and anti-inflammatory properties. Hence, it is useful in skin, respiratory, gastrointestinal, cardiovascular, integument, locomotor and urogenital diseases. It is pharmacologically proven for antibacterial, antiviral, analgesic, anti-inflammatory, antioxidant, sedative, anticancerous properties and effect on cardiovascular and gastrointestinal system. Therefore, this review considerably approves that Sandalwood and its oil have various pharmacological properties. Further, clinical trials are suggested to prove the above mentioned pharmacological activities in various disorders.

ACKNOWLEDGEMENTS

Authors are thankful Ministry of AYUSH for providing all facilities to carry out literature work.

CONFLICT OF INTEREST

None

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