Biological Activities of East Indian Sandalwood Tree, *Santalum album*

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Abstract

The East Indian Sandalwood tree, *Santalum album* L. has been widely used in folk medicine for treatment of 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. With more than 200 constituents, the essential oil is emergent as an interesting and biologically valuable active source of phytochemicals. Therapeutic potentials associated with this oil and its constituents promise future healthcare applications, as shown by recent pharmacological investigations, such as the roles of santalols in combating cancer, tumor, viral diseases, microbes, oxidants, as well as neuroleptic, skin nourishing agent and as dietary factors, thus supporting its traditional uses. The aim of this review is comprehend and put forth, available information on biological activities of this plant from a pharmacological point of view for future directions in clinical applications.

Keywords: *Santalum album* L., essential oil, Ayurveda, biological activity, anticancer, antimicrobial,

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1. Introduction

The East Indian Sandalwood tree, *Santalum album* L. is variously known as the Royal tree (Fox, 2000) and Nature's gift to mankind (Campbell, 1883). *S. album* is a root hemi parasite, woody, tropical species belonging to the taxonomic group Santalaceae. Unfortunately this important tree has become the victim of illegal poaching and spike disease, thus putting down heavily the world production and the rate of loss is so severe that the tree got inducted into the IUCN (International Union for Conservation of Nature and Natural Resources) Red List of Threatened Species, very recently (IUCN, 2012). This forest tree yields the much precious sandalwood oil that contains over 90% santalols (α- and β- santalols and their isomers) and hence is the focus of many research endeavors (Demole *et al.,* 1976). Sandalwood oil is accumulated in the heartwood only after 30 years of its growth under natural conditions (Howes *et al.,* 2004). The essential oil yield from an old matured tree ranges from 2. 5-6% (the highest among all 20 *Santalum* species) depending on the age of the tree, color of the heartwood, individual tree under study, location within the tree and the environment of growth of the tree (Shankarnarayana and Kamala, 1989; Rohadi *et al.,* 2000; Lex, 2006). Moreover the compositions of oils obtained from young and mature sandal trees varies (Shankarnarayana and Parthasarathi, 1984) while the content and composition of oil varies from heartwood sampled at different levels in the tree (Shankarnarayana and Parthasarathi, 1987). Reported essential oil constituents are sesquiterpenoids, triterpenoids (Adams *et al.,* 1975; Demole *et al.,* 1976; Christenson *et al.,* 1981; Ranibai *et al.,* 1986) and phenylpropanoids (Gibbard and Schoental, 1969). Major essential oil components are sesquiterpene alcohols, cis-α-santalol (53%) and cis-β-santalol (23%) (Verghese *et al.,* 1990), α-trans-bergamotol, epi-cis-β-santalol whereas minor constituents include trans-β-santalol and cis-lanceol (Howes *et al.,* 2004), hydrocarbons, α-santalene, β-santalene, α-bergamotene, epi-β-santalene, as α-curcumene, β-curcumene, γ-curcumene, β-bisabolene and α-bisabolol

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(Adams *et al.,* 1975; Braun *et al.,* 2003; Howes *et al.,* 2004; Jones, Ghisalberti, Plummer and Barbour 2006). Alpha-santalol [$C_{15}H_{24}O$, 220.35 Da, CAS No. 11031-45-1, FEMA No. 3006], the major constituent of sandalwood oil, is responsible for most of the biological activities of sandalwood essential oil. The oil costs > 2000 Euro/ kg whereas the estimated global annual requirement is about 10, 000 tons of wood (equivalent to 200 tons of oil), involving a trade of about $ 600 million, of which only 10 % is met from natural resources. On account of its unique sweet, creamy, woody odor with animalic tonalities this essential oil is one of the oldest and most important ingredients for perfumery.

2. Traditional uses

In the Indian traditional medicine system Ayurveda, white sandalwood (=*Chandana*) has largely been used as a demulcent, diuretic, and mild stimulant (Pande, 1977). Sandalwood oil has been traditionally used for treatment of common colds, burns, headaches, bronchitis, fever, infection of the urinary tract, inflammation of the mouth and pharynx, liver and gallbladder complaints and other maladies. The oil finds use in Ayurveda as antiseptic, cooling, diaphoretic, antipyretic, antiscabietic, diuretic, expectorant, stimulant, expectorant, carminative, cicatrisant, antiphlogistic, antiseptic, antispasmodic, aphrodisiac, astringent and in the treatment of bronchitis, psoriasis, palpitations, sunstroke, urethritis, vaginitis, acute dermatitis, herpes zoster, dysuria, urinary infection, gastric mucin augmenting activity, and gonnorheal recovery as it contains antibacterial and antifungal principles (Handa, Kapoor and Chopra, 1951; Okazaki and Oshima, 1953; Winter, 1958; Dastur, 1962; Jain, 1968; Dikshit and Hussain, 1984; Battaglia, 2003). Sandalwood oil along with other plant mixtures has been used to cure stomach illnesses, in treatment of elephantiasis and lymphatic filariasis (Rohadi *et al.,* 2004). The hydrolyzed exhausted sandalwood powder (HESP) on pharmacological screening demonstrated antiremorogenic, antiinflammatory, anti-mitotic,

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antiviral, anticancerous, hypotensive, antipyretic, sedative, ganglionic blocking, and insecticide properties (Shankaranarayana and Venkatesan, 1981; Desai *et al.,* 1991; Brunke, Vollhard and Schmaus, 1995). 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 that have antiinflammatory effect (Holmes, 1989).

In the traditional Chinese medicine (TCM), sandalwood (=*Tan Xiang*) was used by herbalists to treat 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 hearts. The regulating and dispersing action of the oil is curative of the angina pain.

Sandalwood also earns a mention in Discorides' De Materia Medica. Furthermore, the German Commission E monograph suggests 1/4 teaspoon (1–1.5 g) of the sandalwood oil for the supportive treatment of urinary tract infections (Blumenthal *et al.,* 1998) as well as for pains, fevers and strengthening the heart.

3. Anticancer and tumor inhibitory properties

Through a series of manuscripts resulting from investigations of Dwivedi and co-workers, have shown the chemopreventive effects and molecular mechanisms of α-santalol on skin cancer development in both animal models and skin cancer cell lines (Zhang and Dwivedi, 2011). Sandalwood oil has skin cancer chemopreventive effects 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), where α-santalol delayed the papilloma development in both strains of mice (Dwivedi *et al.,* 2003). Alpha-

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santalol at a concentration of 25-75 µM induced apoptotic death of human epidermal carcinoma A431 cells via caspase activation (both dependent and independent manner) together with loss of mitochondrial potential and cytochrome release (Kaur *et al.,* 2005). In a similar study, in female hairless mice strain SKH-1, topical application of α-santalol (5 mg mL^{-1}) demonstrated chemopreventive effects as observed from reduced ornithine decarboxylase activity, tumor incidence, and multiplicity, upon UV-B induced irradiation alone, UV-B irradiation along with DMBA or UV-B irradiation along with TPA promoted tumorigenesis cases (Dwivedi *et al.,* 2006). Moreover, α-santalol was shown to delay skin tumor development, reduced tumor multiplicity, inhibited *in vitro* lipid peroxidation in skin and liver microsomes and hence prevented UVB-induced skin tumor development possibly by acting as an antiperoxidant (Bommareddy *et al.,* 2007). Alpha-santalol (5 mg mL^{-1}) significantly increased apoptosis related proteins, caspases 3 and 8 levels and tumor suppressor protein p53, via an extrinsic pathway in UV B induced skin tumor development model in SKH-1 mice (Arasada *et al.,* 2008). In human prostrate cancer cells, α-santalol induced apoptosis by causing caspases-3 activation (Bommareddy *et al.,* 2012).

About six novel sesquiterpenoids, two aromatic glycosides and several neolignans were identified from sandalwood heartwood chips were evaluated for both *in vitro* Epstein-Barr virus early antigen (EBV-EA) activation in Raji cells, for assessing antitumor promoting activity and *in vivo* two-stage carcinogenesis assays demonstrated its potent inhibitory effect on EBV-EA activation, and also strongly suppressed two-stage carcinogenesis on mouse skin (Kim *et al.,* 2006). Moreover, derivatives of α-santalol demonstrated tumor-selective cytotoxicity in HL-60 human promyelocytic leukemia cells and TIG-3 normal human diploid fibroblasts (Matsuo and Mimaki, 2012). Two lignans obtained from the heartwood samples, demonstrated apoptosis induced tumor cell cytotoxicity against HL-60 human promyelocytic leukemia cells and A549 human lung adenocarcinoma cells, where IC_{50} values were

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determined to be in the range of 1.5- 19.9 μM (Matsuo and Mimaki, 2010). Besides, the aldehyde groups of the lignans were established to be structural requirement for the appearance their cytotoxicity. In fact, terpenoids, the largest class of natural products, have provided traditionally proven anti cancer drugs potentially open for more opportunities in cancer therapy, though reports are mostly restricted to descriptive findings, lack mechanistic insights and systematic structure-activity relationship (SAR) details.

4. Antiviral properties

In an *in vitro* study sandalwood oil demonstrated antiviral activity against herpes simplex viruses (HSV)-1 and 2 in a dose-dependent manner through inhibition of viral replication. It was further assumed that sandalwood oil helped the cells protect themselves by modulating the liver's gluthatione S-transferase and levels of acid-soluble sulfhydryl (Benencia and Courreges, 1999). Sandalwood oil showed inhibitory effect against herpes simplex virus type 2 (HSV-2) *in vitro* on RC-37 cells in a plaque reduction assay and the T_{50} (Toxicity 50) value was determined to be 0.0015% in monolayer cultures of RC-37. 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 (Koch *et al.,* 2008). The virucidal activity of sandalwood has also been established (Xu, 2004). Sandalwood oil constituents, α- and β-santalols, their mixtures and derivatives have been implicated in treatment of warts in human, especially HPV (human papilloma virus) 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. Sandalwood oil has been was

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shown to be used in prevention and treatment of warts, skin blemishes and other viral-induced tumors on skin (Haque and Haque, 2000; 2002). Additionally, sandalwood oil and santalol derivatives were claimed for use in treating cold sores and herpes (Singh and Nulu, 2010). Furthermore, Ayurvedic, traditional Chinese medicine (TCM), and Chakma medicines have been identified as potential sources for novel anti-viral drugs based on different *in vitro* and *in vivo* approaches (Chattopadhyay *et al.,* 2009). Very recently, we demonstrated that single cell and somatic embryo suspension cultures of Indian sandalwood tree grown in air-lift bioreactors and shake-flask cultures as 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 (Misra and Dey, 2013a).

5. Antimicrobial properties

Several studies have focused on the antimicrobial properties of East Indian sandalwood oil (Jirovetz *et al.,* 2006) while many other studies focused on the Australian sandalwood oil (Beylier and Givaudan, 1979). 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 (Viollon and Chaumont, 1994). Furthermore, in another study, maximum inhibitory actions of sandalwood oil were recorded against *Bacillus mycoides* and *Escherichia coli* (Chourasia, 1978). 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* (Chourasia and Tirumala, 1987). 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* (Simanjuntak, 2003). Antimicrobial activity of sandalwood oil against bacterial

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and fungal pathogens revealed MIC values in the range of 50 > 1000 ppm (Morris *et al.,* 1979). 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 in standardized bioassays whereas the unsaponified oil and other kernel components were inactive (Jones *et al.,* 1995). Recently, it was shown that various crude organic fractions and sesquiterpenoid compounds from the oil possessed *Helicobacter pylori* inhibitory properties, the causative organism for gastric cancer and peptic ulcer (Ochi *et al.,* 2005). While probing the *in vitro* activity of 24 essential oils, against the yeast *Candida albicans* ATCC 10231, it was observed that the lowest MIC was recorded for sandalwood oil, i.e. 0.06 % (v/ v) (Hammer *et al.,* 1998). Recently, the antimicrobial activities of different sandalwood essential oils of various origins were studied comparatively, and was concluded that santalols in high and or medium concentrations in sandalwood oils were active volatiles against yeast, gram positive and negative bacteria, and were better antimicrobial agents even in low concentrations (Jirovetz *et al.,* 2006). Recently, the antimicrobial principles were attributed to crude extracts obtained from *in vitro* micropropagated cells and tissues in the form of callus, somatic embryo and seedlings; while immature tree shoots were also shown to be antibacterial as shown by the differential activity against 13 bacterial strains using four screening methods (Misra and Dey, 2012a). However, alcoholic extracts of seeds did not show any antimicrobial activities (Patil *et al.,* 2011), probably indicating the absence of hydrophobic sesquiterpenoid molecules in such polar preparations.

6. Antioxidant properties

Scartezzini and Speroni (2000) have discussed the antioxidant potentials of sandalwood. The *in vitro* antioxidant (at 100-500 mg L^{-1}), and *in vivo* analgesic and anti-inflammatory activities (at 100, 250 and 500 mg kg^{-1}) in mice were established for

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methanolic extracts of heartwood (Saneja *et al.,* 2009). Recently, an anthocyanic pigment cyanidin-3-glucoside from *S. album* was shown to be antioxidant and nutritionally important (Pedapati *et al.,* 2012). 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 (Misra and Dey, 2012b). Sandalwood oil increased glutathione S-transferase (GST) activity and acid soluble sulfhydryl (SH) levels in the liver of adult male Swiss albino mice in oral doses of 5 and 15 µL in 10 and 20 days, respectively (Banerjee *et al.,* 1993). 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 (180 µg mL^{-1}) and DPPH and super oxide free radical scavenging activities (IC_{50} values of 160-191 µg mL^{-1}) in albino mice, there by indicating potential to tackle dementia and memory loss, associated with Alzheimer's disease. Recently, we demonstrated the *in vivo* anti-hyperglycemic and antioxidant potential of sandalwood oil (1 g/kg BW) and its major constituent α-santalol (100 mg/kg BW) in alloxan- and D-galactose mediated oxidative stress induced diabetic male Swiss albino mice models, respectively (Misra and Dey, 2013b).

7. Effects on nervous system

Traditionally, sandalwood has calming and relaxation effect, reduces stress, depression, fear, nervous exhaustion, anxiety, and enhances meditation, this way; the healing process can be hastened as the person loses their worries and discomfort. Furthermore, 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 (Battaglia, 2007). Santalols have been reported to have central nervous system (CNS) depressant effects such as sedation, and they affected sleep-wake cycle in sleep-disturbed rats, such as decreased

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walking time and increase in non-rapid eye movements. Results suggested action of santalols via circulatory system by adsorption into the blood through respiratory mucosa, hence demonstrating implication in patients having sleep related difficulty (Ohmori *et al.,* 2007). In a first of its kind study, olfactory receptor neurons were identified that were specifically stimulated by four synthetic sandalwood compounds and oil, neurons which expressed endogenous olfactory receptors with ability to discriminate between sandalwood odorants with slight differences in their molecular structures, in rats, by monitoring fluxes in internal calcium concentrations (Bieri *et al.,* 2004). Sandalwood oil affected the motility of mice upon inhalation, and hence was noted to be sedative in female Swiss albino mice, at 40 % compared to untreated ones. Furthermore, solvent extracts of heartwood were shown to have neuroleptic property in mice through *in vitro* and *in vivo* assay systems. 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 intragastric and intracerebroventricular routes of administration (Okugawa *et al.,* 1995). Alpha-santalol was shown to be a strong antagonist of dopamine D2 and serotonine 5-HT2A receptor binding. Furthermore, the effect of alpha-santalol, was the same as that of chlorpromazine as an antipsychotic agent (Okugawa *et al.,* 2000). Alpha-santalol caused significant physiological changes such as relaxing and sedative effects, whereas sandalwood oil provoked physiological deactivation but behavioral activation after transdermal absorption (Hongratanaworakit *et al.,* 2004). Furthermore, we have recently reported that TLC-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 this essential oil for use in the treatment of Alzheimer's disease, as well as in skin-care (Misra and Dey, 2013c).

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8. Effects on body physiology

Inhalation of sandalwood oil improved hearing environmental sounds (Sugawara *et al.,* 1999). Sandalwood oil and α-santalol affected several physiological parameters, as well as self-ratings of arousal (alertness, attentiveness, calmness, mood, relaxation and vigor). Alpha-santalol produced higher ratings of attentiveness and mood than sandalwood oil alone. Sandalwood oil elevated pulse rate, skin conductance level and systolic blood pressure where as α-santalol elicited higher ratings of attentiveness and mood than what sandalwood oil or the placebo did. Correlation analyses revealed that these effects were mainly attributed to perceived odor quality, thus suggesting a relation between differences in perceived odor quality and arousal levels (Heuberger *et al.,* 2006). Recently, sandalwood tea was demonstrated to have significantly increased the myocardial contractility and heart rate of the isolated and failed frog heart, while it showed good effect as anti-fatigue in significantly contracting the smooth muscle of isolated rabbit aortic strips (Qin *et al.,* 2010). Sandalwood oil did not demonstrate any phototoxic effects (Katz, 1946; Urbach and Forbes, 1972), although occasional cases of irritation or sensitization reactions in humans are reported (Burdock and Carabin, 2008).

9. Effects on metabolism

Trans-mammary exposure of suckling mouse pups to sandalwood oil showed changes in neonatal hepatic xenobiotic metabolizing enzymes. Furthermore, it was observed that sandalwood oil constituents and its metabolites 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 (Chhaabra and Rao, 1993).

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10. Uses as dietary factors

The long history of oral use of sandalwood oil in dietary supplements was without any reported adverse effects and was considered safe as a flavor ingredient with a daily consumption at present usage levels of 0.0074 mg kg^{-1} (Burdock and Carabin, 2008). Oral feeding of diets enriched with sandalwood seed oil (containing 30-35% ximenynic acid) to female rats for eight weeks showed marked relative increases of 16:0 and 18:1(n-9) acid content in adipose and liver tissues compared to rats that were fed a standard laboratory animal diet or oil rich diet (Liu and Longmore, 1997). 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 (Guo *et al.,* 2010). Furthermore, it was recently shown that leaf extracts of sandalwood tree demonstrated antihyperglycemic and antihyperlipidemic effects in streptozotocin induced diabetic rats (Kulkarni *et al.,* 2012).

11. Genotoxicity effects

The DNA damaging activity of sandalwood oil, in *Bacillus subtilis* was studied in a spore Rec assay using the strains H17 Rec^+ and M45 Rec^- in the presence or absence of metabolic activation and was found to be non-genotoxic (Ishizaki *et al.,* 1985). Similarly, sandalwood oil-induced inhibition of *B. subtilis* in spore Rec assay and was found to be non-genotoxic (Watanabe, 1994).

12. Effects on respiratory system

The soothing and demulcent effects of sandalwood oil have been used to treat respiratory tract infections, specifically chronic bronchitis involving chronic dry cough (Holmes, 1989; Lawless, 1992; Mojay, 1996; Davis, 1999). However clinical trials data are

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not available for these activities, thus providing opportunities for further clinical and *in vivo* studies.

13. Effects on genitourinary system

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 (Holmes, 1989; Lawless, 1992; Mojay, 1996; Davis, 1999). 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.

14. Effects on integumentary system

The emollient properties of sandalwood render it useful in skin care. Sandalwood oil is soothing, cooling and moisturizing for dry skin conditions caused by dryness and inflammations. Besides, the oil has been used to relieve eczema, psoriasis and for the treatment of oily skin and acne (Lawless, 1992; Mojay, 1996; Davis, 1999).

15. Insecticidal activities

Sandalwood oil acts as a repellent of the pest *Varroa jacobsoni* Oud. (Imdorf *et al.,* 1999), in honey bee colonies and has been used as an acaricide. Against *Lycoriella mali* (the mushroom fly), a modest activity was reported (Choi *et al.,* 2006). The oil is also impenetrable to termites (Kaikini, 1969; Srinivasan *et al.,* 1992). Besides, santalol was shown to be active against spider mites *Tetranychus urticae* by virtue of its acaricidal and oviposition deterring effects (Roh *et al.,* 2011; Roh *et al.,* 2012)

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16. Future directions

The phytochemistry of heartwood constituents, more than 200 of them, reported from several sandalwood species have been reviewed extensively (Baldovini *et al.,* 2011). Newer sesquiterpenoid constituents i.e., santalyl formates (Hasegawa *et al.,* 2011) are being discovered every year. Very recently, sandalwood essential oil was shown to be among one of the stronger essential oils to demonstrate mammalian DNA polymerase (*pol*) inhibitory, cancer cell (human colon carcinoma, HCT116) growth inhibitory, antiallergic, and anti-β-hexosaminidase release activity in rat basophilic leukemia RBL-2H3 cells treated with calcium ionophore A23187, and antioxidant activity by a lipophilic-oxygen radical absorbance capacity method (Mitoshi *et al.,* 2012). Majority of these biological activities have been attributed to the santalene type sesquiterpenoids, i.e., α- and β- santalenes and santalols. Incidentally, several genes and encoded enzymes responsible for santalene biosynthesis have been cloned and characterized recently (Jones *et al.,* 2011). Similar genetic approaches would enable further understanding of the biosynthetic routes, phytochemical diversity of bioactive santalols, whereas microbial metabolic engineering approaches might pave the path to obtain desirable diversity and quantities of sandalwood sesquiterpenoids for the flavor and fragrance industry (Jones *et al.,* 2008). Moreover bioinformatics approaches and softwares have been developed for prediction and detection of natural products from genomic sequences in addition with other –omics data, to facilitate industrial high-throughput screening in drug discovery (Fedorova *et al.,* 2012). With global demands sky rocketing with every passing year, *in vitro* biotechnological means of micropropagation might add up as critical bioresource to obtain bioactive constituents (Misra and Dey, 2012). The improved analytical tools and techniques developed such as multidimensional gas chromatographic system (MDGC), equipped with simultaneous flame ionization and mass spectrometric detection (FID/MS) (Sciarrone *et al.,* 2011) and Near Infrared (NIR) spectroscopy with

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chemometric techniques for detection of adulterants (Thankappan *et al.,* 2010; Kuriakose and Joe, 2012) have provided essential resources for advanced and rapid research in sandalwood oil and wood. Furthermore, it has been recently stressed upon 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 (Katiyar, *et al.,* 2012). Besides, drug discovery and development need not always be confined to new molecular entities, but traditional herbal formulations and botanical drug products with robust scientific evidence can also be alternatives (Patwardhan and Mashelkar, 2009), thus accelerating the clinical candidate development using reverse pharmacology approaches (Patwardhan and Vaidya, 2010).

17. Conclusions

For more than a century, the study of sesquiterpenoids in sandalwood tree have challenged the ingenuity and technical skill of chemists and biochemists interested in the structure, chemistry, synthesis and biological origins of this marvelously varied group of compounds. With recent upsurge in research endeavors to verify the traditional healthcare uses by experimental approaches either *in vitro* or *in vivo*, have provided impetus to in depth pharmacological and mechanistic investigations for the essential oil constituents, and eventual clinical trials.

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